EUROTHERM® FLEXIBLE SOLUTIONS

Life Sciences

CATALOGUE

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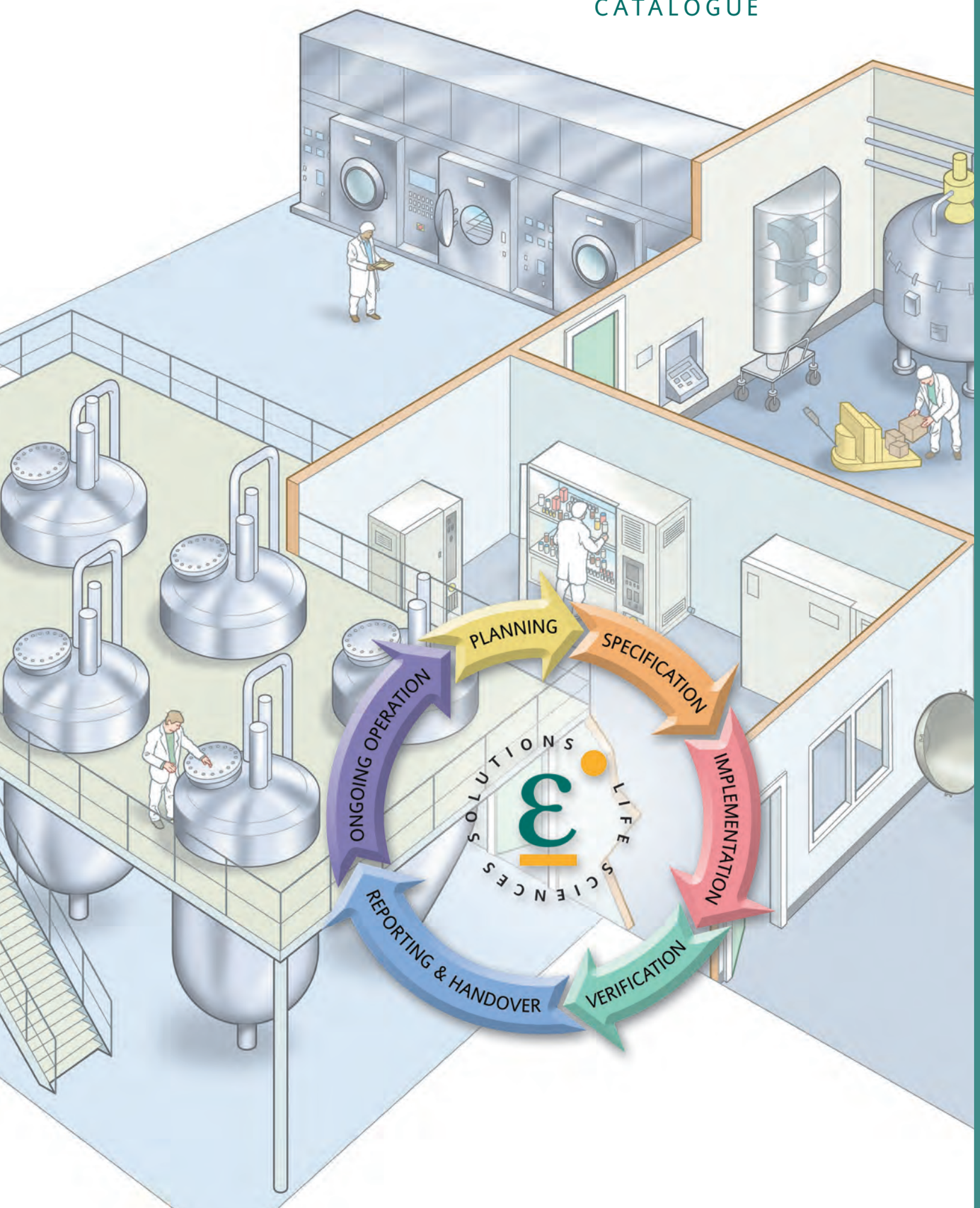
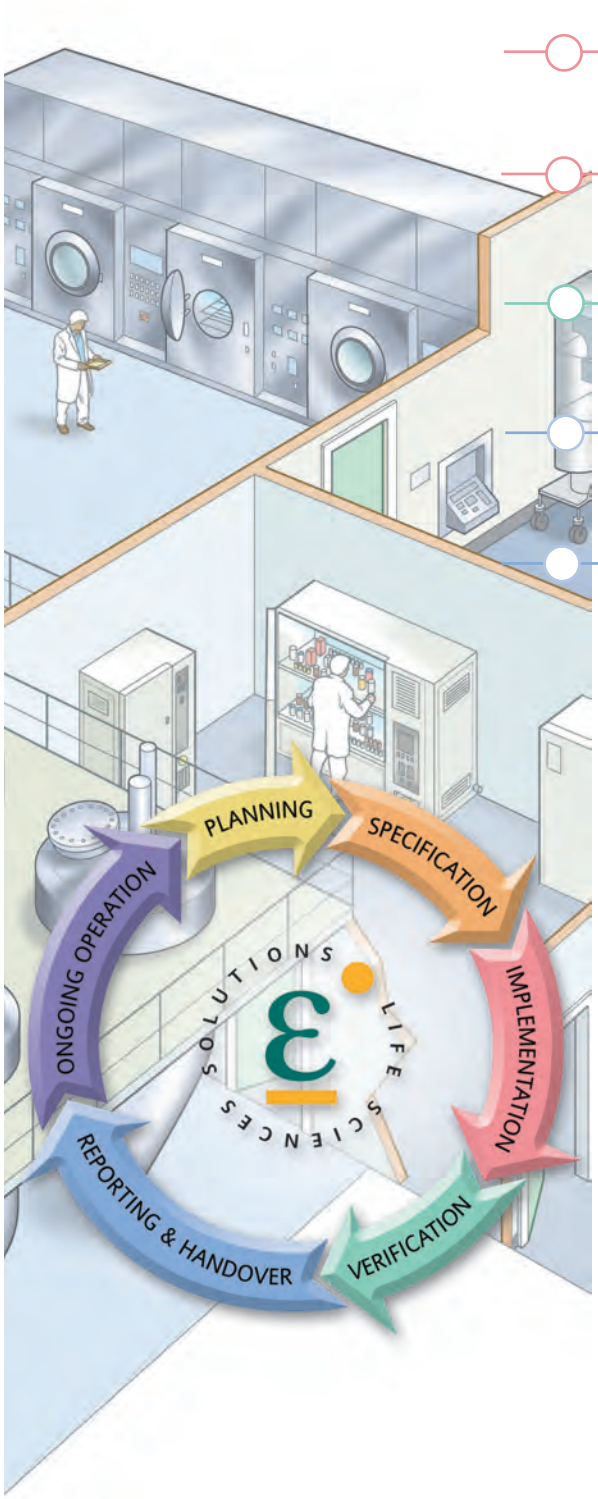


Life Sciences CATALOGUE



INTRODUCTION

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EUROTHERM ENGINEERING SERVICES

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APPENDIX 1

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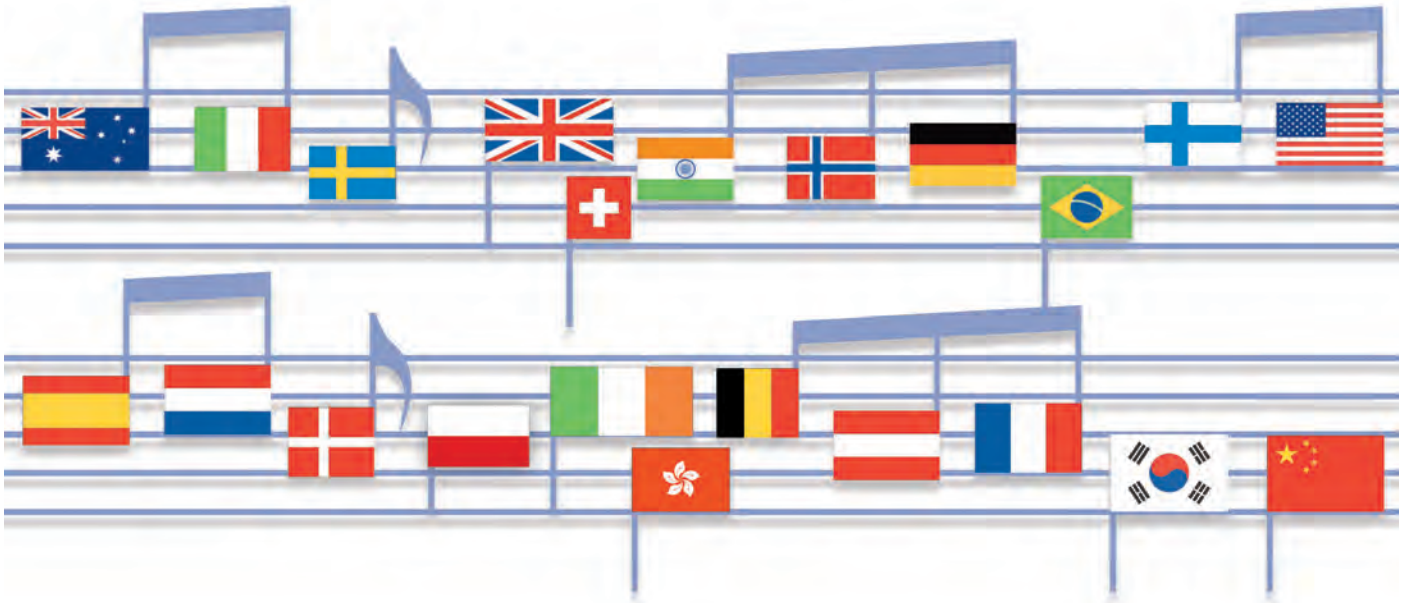
Eurotherm: International sales and service

Understanding and providing local support is a key part of Eurotherm business. Complementing worldwide Eurotherm offices are a whole range of partners and a comprehensive technical support team, to ensure you get a service you will want to go back to.



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ED57

Eurotherm is also represented in the following countries:

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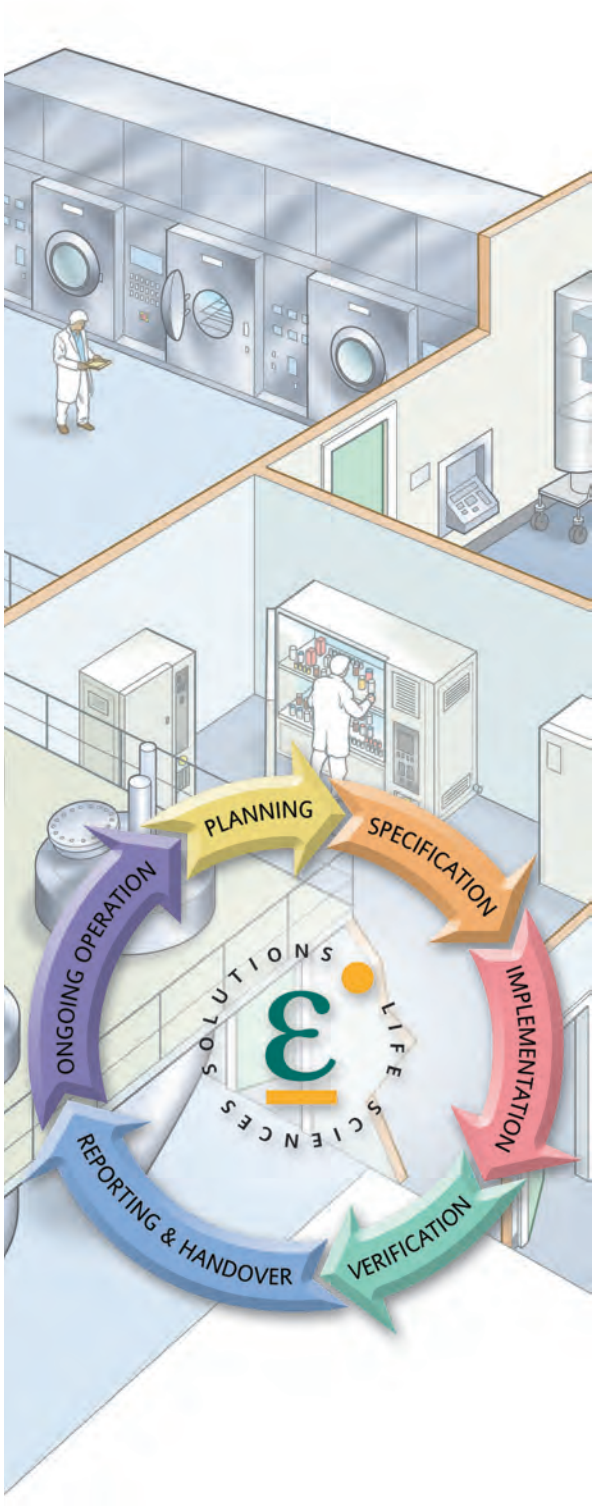
Azerbaijan
Bahrain
Bangladesh
Benin
Bosnia and Herzegovina
Bulgaria
Burkina Faso
Cameroon
Canada
Czech Republic
Egypt
Georgia
Greece
Guinea-Conakry
Hungary
Indonesia
Israel
Ivory Coast
Japan
Jordan
Kazakhstan
Kenya
Kuwait
Latvia
Lithuania
Malaysia
Mali
Mexico
New Zealand
Niger
Nigeria
Oman
Pakistan
Philippines
Puerto Rico
Qatar
Romania
Russia
Saudi Arabia
Serbia and Montenegro
Singapore
Slovak Republic
Slovenia
South Africa
Sri Lanka
Thailand
Togo
Tunisia
Turkey
Turkmenistan
UAE
Ukraine
Uzbekistan

Represented by:

Life Sciences CATALOGUE

INTRODUCTION



Eurotherm® - The Life Sciences Solutions Provider

Why Eurotherm?

Eurotherm is a solutions provider that specialises in improving efficiency of plant operation and compliance with regulatory bodies e.g. FDA, EMEA.

- Global expertise and experience in providing Pharmaceutical and Biotech solutions
- Proven track record in rapidly delivering solutions with optimum ROI
- More than 40 years experience in control, data management and scalable automation solutions
- Cost-effective solutions to improve the reliability and efficiency of your processes throughout their life cycle
- Proven experience in working and integrating with multiple suppliers and platforms
- Specialist teams with comprehensive experience in validating systems
- Global expertise, local supply and support
- A team to work with your team a partnership for success

Confidence in Validation

Eurotherm understands the importance and complexity of validation and can reduce the cost, time and confusion of the regulatory processes.

- Successful completion of validated solutions around the world
- Experienced, dedicated, specialist teams
- Active responses to latest regulatory developments e.g. PAT
- 'Test and validate once - use many times' engineering strategy
- Built-in 21 CFR Part 11 features
- "Wrap and comply" solution upgrade validation path
- Standard validation templates

Confidence in measured value for your money

Eurotherm are committed to developing products and services specifically for the Life Sciences industry continually minimising cost and maximising productivity.

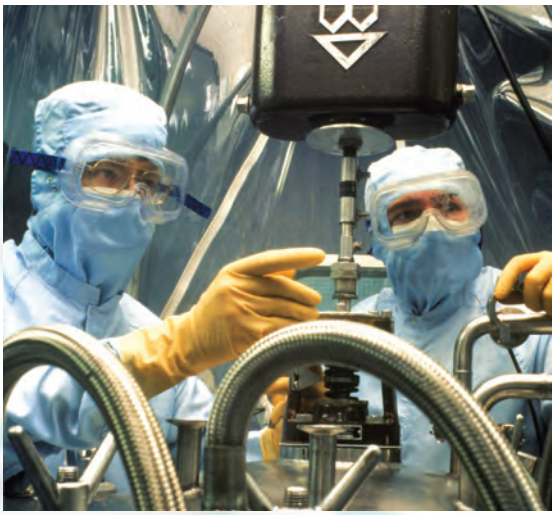
- Consultancy services to ensure you get exactly what you need
- Consultancy to help you reduce validation time, costs and confusion
- Global and plant wide consistency – re-using engineering to minimise costs
- Complete life cycle support – maximising productivity and efficiency
- Lifetime service level agreements to protect your investment
- A complete range of services designed to provide you with the best value from your system –
  - *Installation*
  - *Commissioning*
  - *Training*
  - *Calibration*
  - *Spares management*
  - *Technical support*

Life Sciences solutions to lower production costs

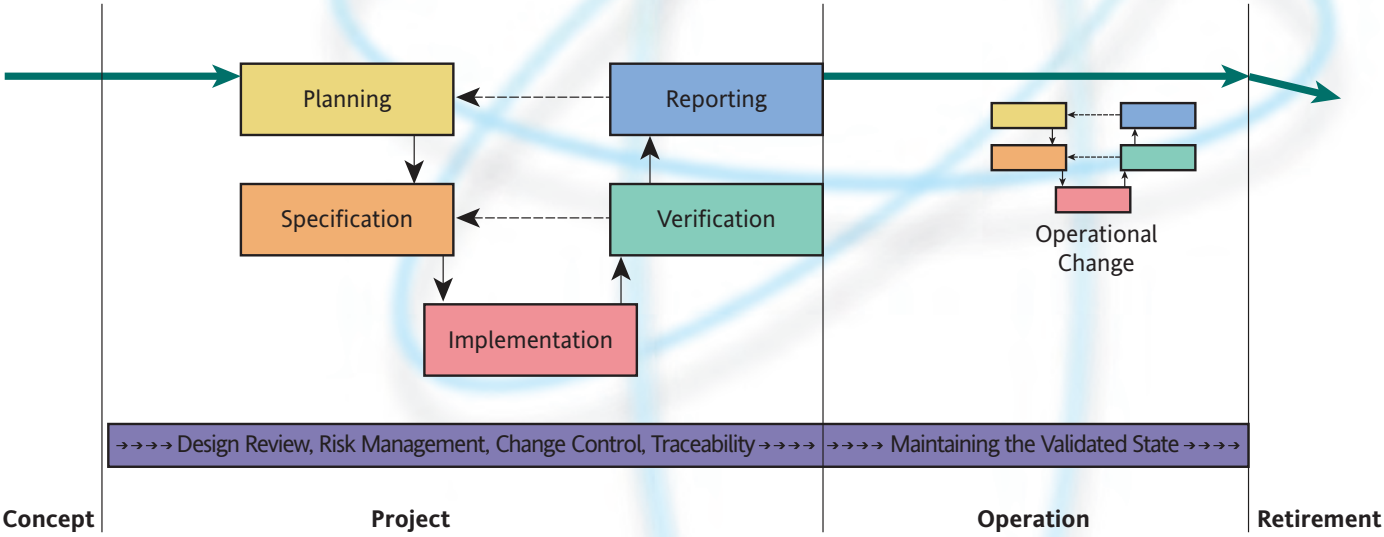
Eurotherm provide engineered solutions for plant automation throughout the world. Our hardware and software expertise can provide you with a solution to match your manufacturing requirements and maximise efficiency, productivity and ultimately your return on investment.

Eurotherm Life Sciences team can provide you with:

- Automation and application expertise and experience
- World-class accuracy of control
- World-class secure data recording
- Delivery of proven solutions
- Scalable solutions – from lab to pilot to full production
- Rapid time to market
- Batch control with automatic tracking and traceability



GAMP LIFECYCLE



What does this mean to your production?

- Rapid return on investment
- Lower manufacturing costs
- Reduced labour costs and SOPs through automation
- Improved plant availability through redundancy options
- Reduced cycle times and improved asset utilisation
- Tighter tolerances to improve product quality and consistency
- Maximised efficiency and minimised production waste and interruption
- Reduced manual processes and improved data security through automatic data gathering

Full Life Cycle Support

Eurotherm use a Life Cycle Development approach based on GAMP5 to ensure consistent control and quality worldwide. This results in a reduction in validation costs and provides full control and traceability throughout the project lifecycle.

From Conception to Retirement - Why Eurotherm?

- Strategic, long-term, global partner
- A complete service. A complete solution
- Quality engineering services
- Specialist application expertise
- World-class, scalable solutions

Planning

- Feasibility studies
- Assistance with GxP risk management
- Assistance with requirements capture and formal URS creation
- Validation audits
- Formal quality planning based on GAMP5 lifecycle

Specification

- High quality documentation based on GAMP5 templates – supplier documentation can be leveraged with zero repeated effort by the end user

Implementation

- Scalable DCS solutions
- Total plant data management
- Advanced control systems
- Full range of configuration and cooling services
- Code review
- Installation and commissioning services

Verification

- Module test, integration test, factory and site acceptance test are all executed to GAMP5 guidelines and can be leveraged to reduce end user qualification effort

Reporting & Handover

- Formal quality report and handover checklist confirms fitness of the system for its intended purpose

Ongoing Operation

- Service level agreement
- Training
- Spares management
- Back-up and disaster recovery
- Periodic review assistance
- Change management services
- Assistance in decommissioning
- Data recovery

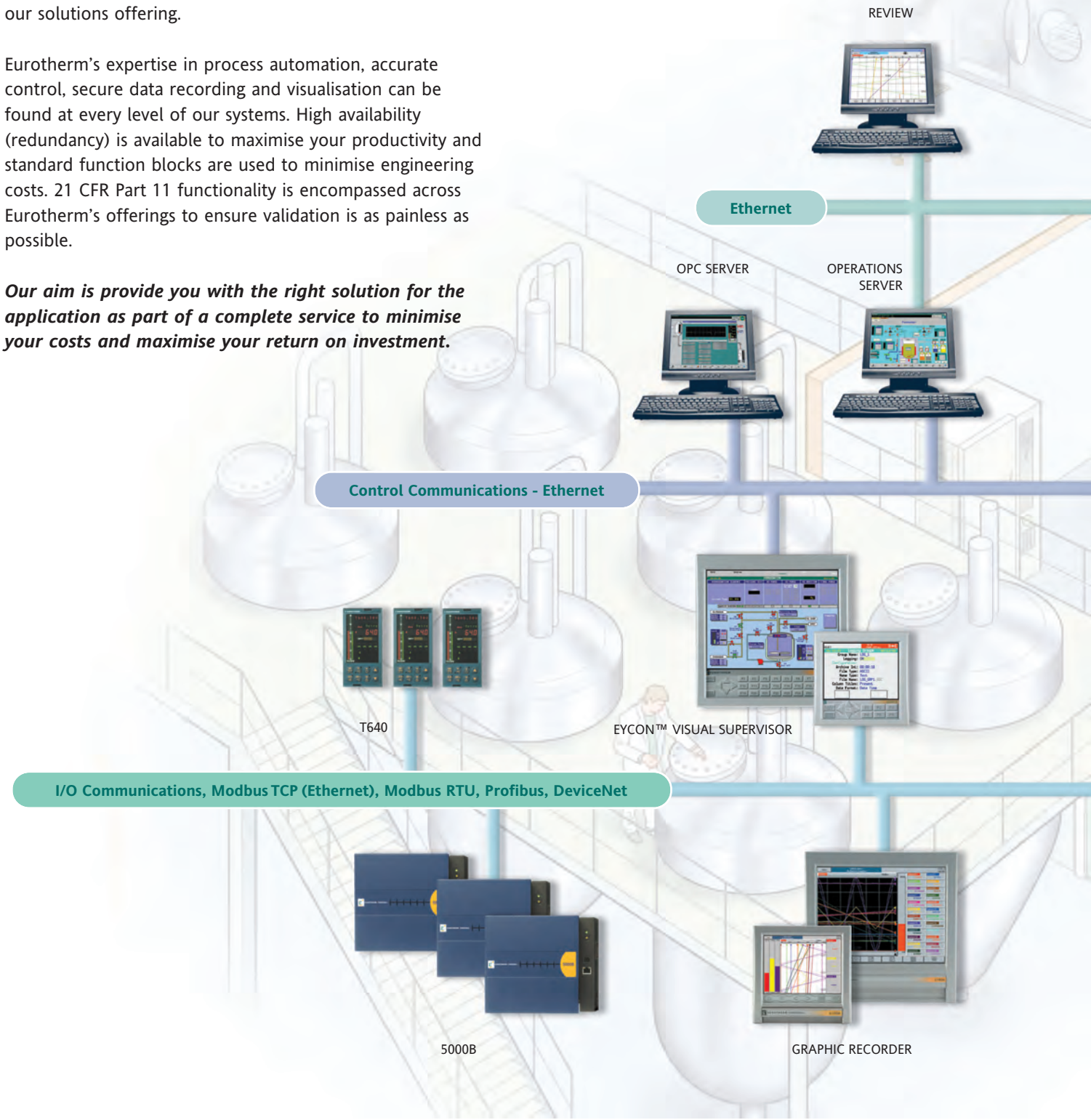
Modular, scalable solutions from lab to pilot to full production

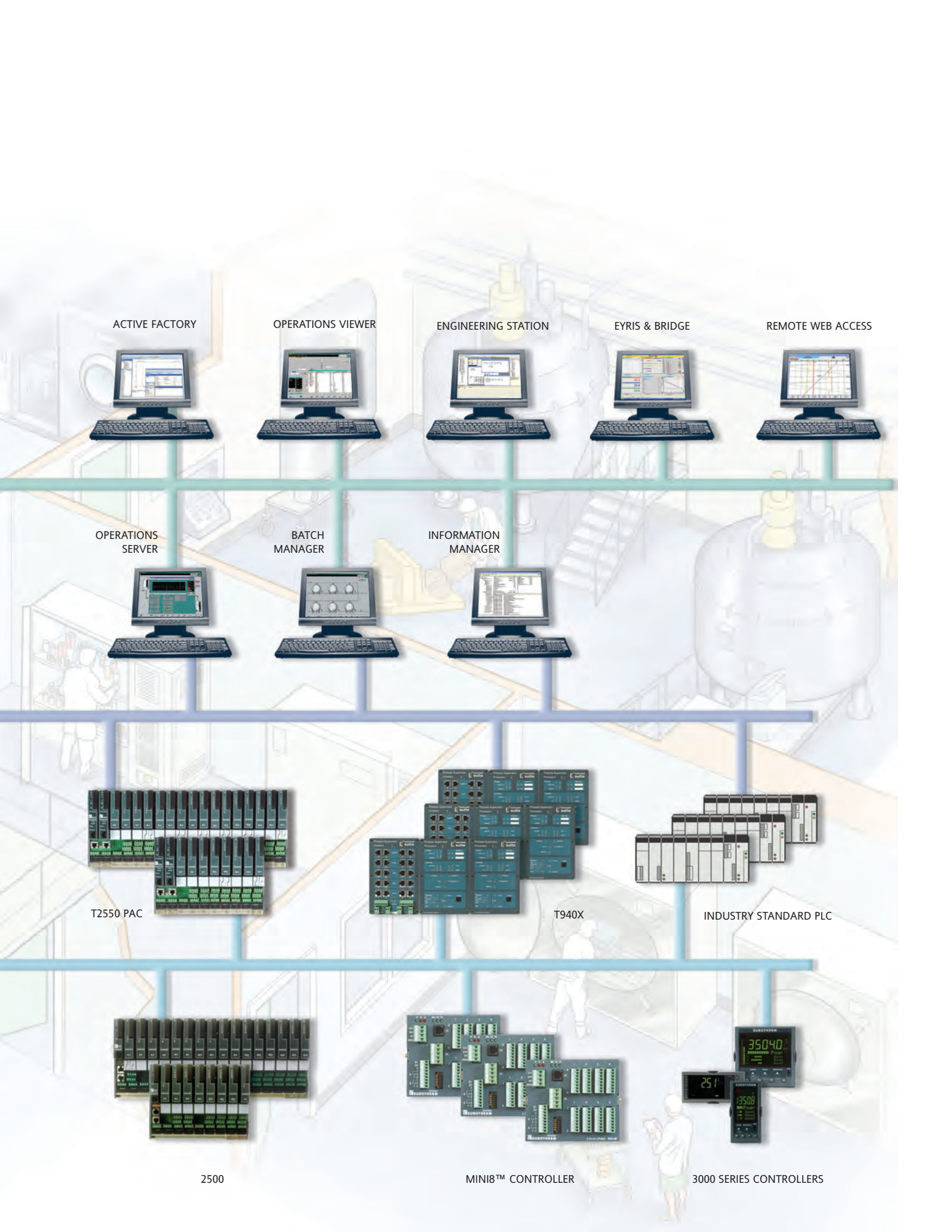
From simple loop control to information integration and plant wide DCS systems, Eurotherm can offer scalable, modular solutions to match your application and budget. As your requirements grow, new modules can be easily incorporated into your system

Integration is a key part of Eurotherm's offerings. Our products are designed to work on multiple communication platforms with connectivity at all levels. Where appropriate or necessary, 3rd party integration is an established part of our solutions offering.

Eurotherm's expertise in process automation, accurate control, secure data recording and visualisation can be found at every level of our systems. High availability (redundancy) is available to maximise your productivity and standard function blocks are used to minimise engineering costs. 21 CFR Part 11 functionality is encompassed across Eurotherm's offerings to ensure validation is as painless as possible.

Our aim is provide you with the right solution for the application as part of a complete service to minimise your costs and maximise your return on investment.




ACTIVE FACTORY
OPERATIONS VIEWER
ENGINEERING STATION
EYRIS & BRIDGE
REMOTE WEB ACCESS
OPERATIONS SERVER
BATCH MANAGER
INFORMATION MANAGER
T2550 PAC
T940X
INDUSTRY STANDARD PLC
2500
MINI8™ CONTROLLER
3000 SERIES CONTROLLERS

Minimising validation costs

With ever-changing global regulatory requirements for the Life Sciences Industries, it is our vision and direction to help our customers to get products to market safely and in a timely manner, while adhering to the relevant regulatory requirements.

Can Eurotherm really reduce your costs?

- To reduce costs, a real understanding of regulatory requirements is needed – we have specialist engineers dedicated to following global regulations
- Through standardisation we minimise customisation, our products have built-in features to meet regulations such as 21 CFR Part 11, PAT
- Our Life Sciences Consultants work closely with our product development teams to continuously follow and implement the latest regulatory requirements within our solutions
- Proven, standard validation templates based on GAMP5

You can be confident that Eurotherm is the right partner for your validation needs...

- Successful completion of validated systems around the world
- Involvement in major Life Sciences professional organisations e.g. ISPE, GAMP, ISA
- Customers have experienced significant reductions in validation costs by engaging Eurotherm at the beginning of a project and resolving multiple issues before manufacturing begins
- Successful audits by numerous major Pharmaceutical and Biotech companies
- All products are manufactured and tested to ISO9000 and TickIT

Wrap & Comply

It is not always necessary to replace your legacy systems to comply with current regulations...

With the "Wrap & Comply" concept we are looking at working with your current system components to minimise the validation effort. Maximising the re-use of hardware and software will enable you to "Wrap" your legacy system in a compliant architecture in order for the GxP system to "Comply" with regulatory requirements including 21 CFR Part 11.

Save time and money...

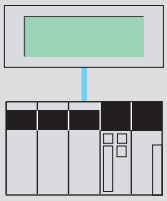
- Re-use existing hardware
- Re-use existing software
- Minimise SOPs
- Improve plant efficiency and quality
- Faster time to market
- Reduce validation

Our team of experience engineers are available to work with you and assist you to identify the non-compliant systems and take the necessary remediation action to validate them:

- **Gap Analysis** – Identify computer system validation gaps
- **Coverage Assessment** – Determine which GxP rules must be satisfied
- **Risk Assessment** – Determine and prioritise potential compliance actions
- **Mitigation/Remediation Plan** – Formulate a corrective action plan addressing the deficiencies following the rule: "Maintain as much of the existing hardware and software possible"
- **Implementation** – Implement corrective actions

Wrap and Comply: Expand, enhance, comply...

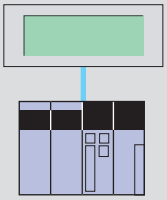
Non Compliant...



PROBLEM...

Standalone legacy system connected to a simple HMI with no security installed before 1997 (no changes or very minor changes made since).

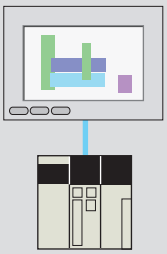
- The equipment is reliable and still supported by the original manufacturer
- There is no requirement for additional functionality
- SOPs are in place to manage change control of day to day operations and program changes. Your staff are trained in the operation and SOPs



PROBLEM...

Existing standalone legacy system connected to a simple HMI with no security. Risk analysis and/or company standards require Electronic Records and Signatures.

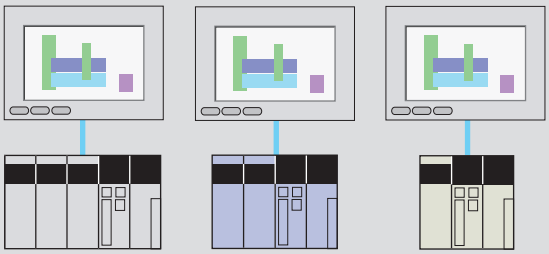
- The equipment is reliable and still supported by the original manufacturer
- There is a requirement for a small number of additional sensor inputs to increase quality and visibility of the system
- SOPs are in place to manage change control of day to day operations and program changes. Your staff are trained in the operation and SOPs



PROBLEM...

Existing standalone legacy system connected to a HMI with no security. Risk analysis and/or company standards require Electronic Records and Signatures.

- The equipment is reliable but there is reducing support from the original manufacturer
- There is a requirement for a larger expansion of the process and/or a need for additional data and implementation of PAT
- SOPs are in place to manage change control of day to day operations and program changes. Your staff are trained in the operation and SOPs



PROBLEM...

You have systems from multiple manufacturers, islands of automation and limited communication between systems. Risk analysis and/or company standards require Electronic Records and Signatures.

- The equipment is reliable but there is reducing support from the original manufacturer
- There is a requirement for a larger expansion of the process and/or a need for additional data and implementation of PAT
- SOPs are in place but there are issues managing numerous audit trails and multiple security systems
- Systems have different programming languages

...Compliant

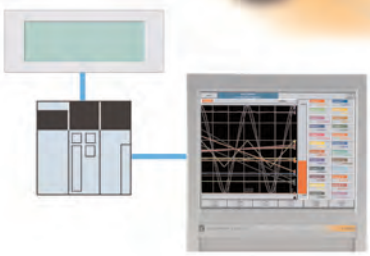
...SOLUTION

No changes are necessary.
With changesmade to
21 CFR Part 11 many systems
are going to fall into this category.
We recommend no change.

...SOLUTION

Adding a Chessell™ Graphic Recorder will provide compliant data logging by acquiring signals from new sensors.
The Eurotherm solution is:

- Cost effective
- Easy to implement and validate (configuration vs programming)

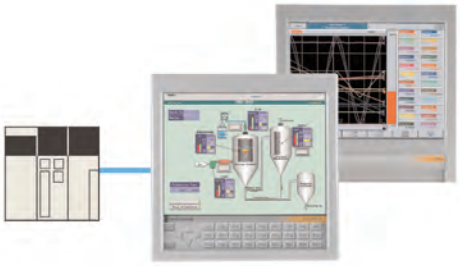


...SOLUTION

Replace the operator interface with a compliant graphic recorder and data acquisition unit or the Eycon™ Visual Supervisor.

The Eurotherm solution provides:

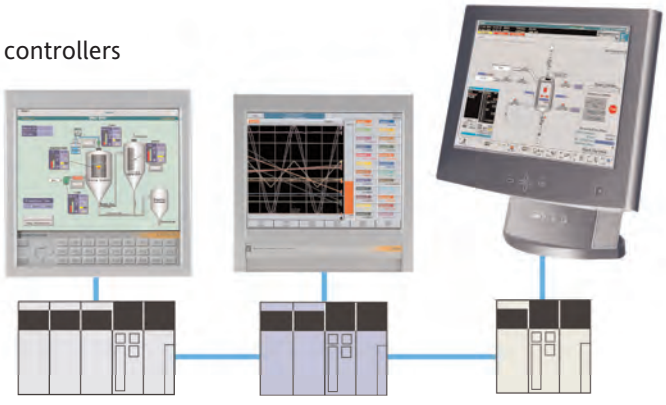
- HMI, security and control integrated all in one
- No change of control strategy (preserves validation)
- An opportunity to enhance the operator interface
- Local storage of secure process data
- Recipe, batch and set-point programming as standard



...SOLUTION

Eurotherm have a program to upgrade all of your controllers offering all of the benefits and features plus:

- One security regime (expired passwords need changing in just one place)
- One place for all audit trails (no more searching right one)
- Programs for all systems checked and compared the running system



21 CFR Part 11 made easy

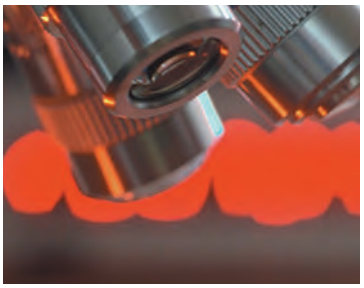
Eurotherm has a range of products that are designed to meet regulations such as 21 CFR Part 11. From plant wide data access security management to single, secure recorders, we can provide a solution that is right for you.

Solutions designed for ease of use and validation

- Minimise validation time and testing by using standard, built-in features to meet 21 CFR Part 11 that can be configured to your requirements
- Data recording at every level, local and plant wide
- Never lose data with cost-effective multiple recording and secure back-up
- Centralised security system allowing maintenance of user accounts and passwords from one or multiple locations
- Secure local data collection with automatic archiving across the network – truly designed to keep data safe
- Remediation solutions for legacy systems – **"Wrap & Comply"**

Electronic Records

- Secure process values and audit trails (alarms, events, operator actions, log-in/log-out, operator notes, electronic signatures)
- Protection of data through binary, compressed and check-summed records
- Accurate time stamps are ensured using automatic Time Synchronisation to a known clock source
- Provision for electronically copying data for archive
- Export facility allowing viewing of secure records in human readable form
- Store and forward
- Review and approve facility



Electronic Signatures

- All user actions can be configured to require signing or require signing and authorisation
- User specific access according to authority level
- Signature element controls unique user signature, password expiry, minimum password length, automatic log-off, automatic disabling and notification of failed login attempts
- Ensuring unique users by retiring and not deleting accounts

Central Security Manager with Full Audit Trail –

Security Manager offers significant operation cost savings and ease of use by allowing maintenance of user accounts and passwords from one or multiple locations. If a user needs to change their password they can do so on a local instrument or PC and this will be automatically distributed across all systems to which they have access.

- A common security tool across multiple product ranges
- Change in one place, deploy to many
- Support for multiple security zones
- Built-in audit trail for 21 CFR Part 11 validation
- Automatic version control
- Support for electronic signatures

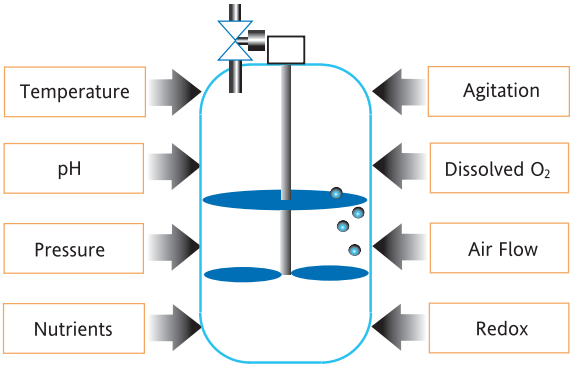
Strength through wide-ranging application experience

Our range of application experience could help you to increase productivity and lower costs. All of our solutions into the Life Sciences industry are flexible and scalable to suit the process exactly and have built-in 21 CFR Part 11 features.

Example applications

FERMENTATION PROCESS

- Precise loop control
- Sequential control for vessel sterilisation and more complex control strategies
- Recipe management with easy parameterisation
- Batch control and reporting
- Setpoint programming
- Alarm management
- Secure collection of on-line data from the fermenter system for analysis



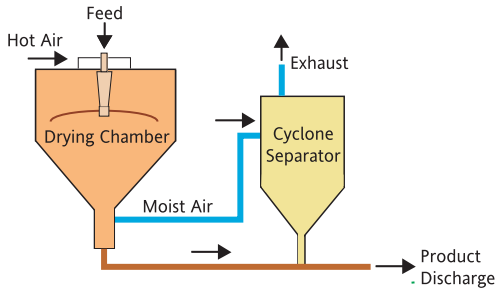
Incubation control necessitates the precise control of a number of parameters – of primary importance are:

- Temperature
- pH
- DO2
- Agitation
- Pressure
- Foam control
- Auxiliary feed

SPRAY DRYING PROCESS

The challenges facing both designers and users are to increase production, improve powder quality and reduce costs in the spray drying process. This requires an understanding of the process and a robust control implementation - Eurotherm can help you to meet these challenges.

- Spray Drying phases:
- Feed preparation
- Atomisation
- Drying
- Separation of powder from moist gas
- Cooling and packaging

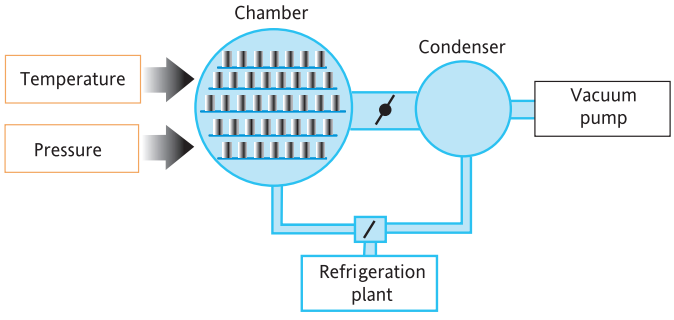


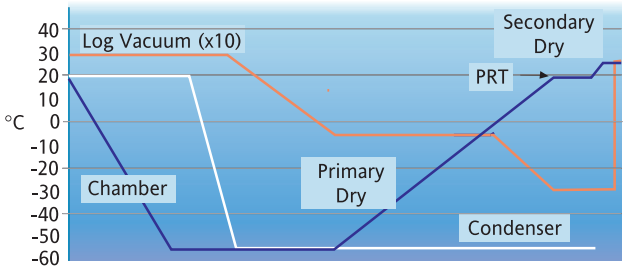
Accurate and repeatable control of the spray drying process requires a flexible control solution.

- Precise loop control with setpoint profile programming
- Recipe management system for easy parameterisation
- Sequential control for complex control strategies
- Secure data recording for analysis and evidence
- Local operator display with clear graphics and controlled parameter access

FREEZE DRYING

- Precise temperature control with ramping
- Sequential control of temperature, vacuum and the refrigeration plant – both for freeze drying and sterilisation
- Safety strategies to ensure product is not damaged as a result of plant failure
- Data recording for analysis and evidence





ENVIRONMENTAL AND STABILITY CHAMBER MONITORING AND CONTROL

- Multiple room monitoring with local logging capability
- Mean Kinetic Temperature calculation
- Selectable stability testing period
- Selectable sampling frequency
- Sophisticated alarm functionality
- Accurate continuous and sequential control
- Report generation
- SMS or email alerts triggered by alarms or events

$$T_k = \frac{\frac{-\Delta H}{R}}{\ln\left[\frac{e^{\frac{-\Delta H}{RT_1}} + \cdots e^{\frac{-\Delta H}{RT_n}}}{n}\right]}$$

T_k being the mean kinetic temperature in Kelvin
ΔH is the heat activation in kjoule per mole
R is the universal gas constant in kjoule per mole per Kelvin
T_1 and T_n are the temperature samples for periods 1 and n, respectively
n is the total number of periods in the calculation

STERILISATION PROCESS

- Autoclave control and monitoring
- Batch control and reporting
- Pass/fail indication
- Local, custom graphic displays
- Secure data collection

MIXER/BLENDER CONTROL

- Precise loop control with setpoint profile programming
- Recipe management system
- Sequential control
- Secure data recording for analysis and evidence
- Local operator displays with custom graphics to best suit the process

WATER PURIFICATION

There are a number of methods commonly used to purify water. Their effectiveness is linked to the type of contaminant being treated and the type of application the water will be used for:

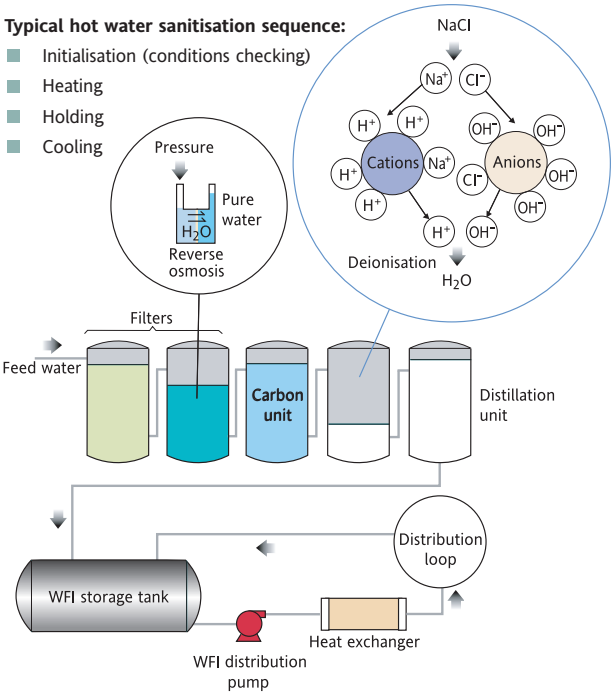
- Filtration
- Distillation
- Activated carbon adsorption
- Deionisation (ion exchange)

Hot Water Sanitisation

Sanitisation of water purification equipment with hot water is achieved via an appropriate combination of exposure time and temperature.

Typical hot water sanitisation sequence:

- Initialisation (conditions checking)
- Heating
- Holding
- Cooling

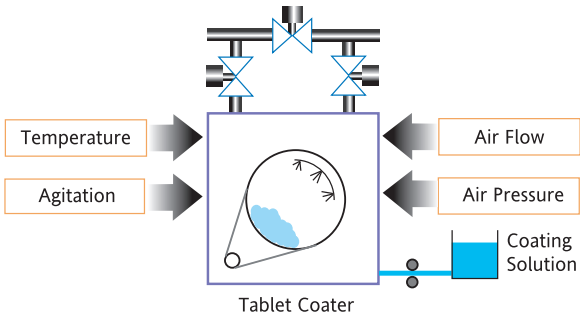


Flexible, accurate and repeatable control:

- Precise loop control with setpoint profile programming
- Sequential control for sanitation/sterilisation
- Onscreen operator messaging
- Duty/standby pump control
- Secure data recording

TABLET COATING

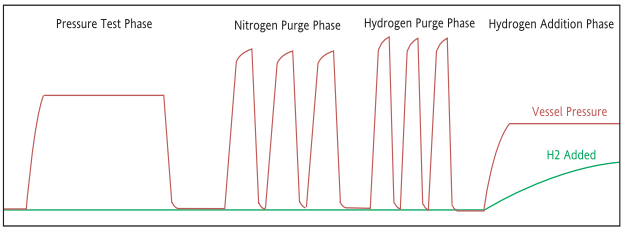
- Batch identification and recipe selection (film or sugar coating)
- Loading/dispensing (accurate dosing of required raw materials)
- Accurate, repeatable control of the coating environment
- Secure collection of on-line data from the coating system for analysis and evidence



Tablet Coater

HYDROGENATION PROCESS

- Sequential control for vessel pressure testing, purging and hydrogen addition
- Precise loop control for temperature and pressure
- Secure data collection from the hydrogenation process
- Local operator display with clear graphics and controlled access



Eurotherm products: The most complete set of products for Life Sciences solutions from a single supplier

DCS Operations Viewer and Server

Enhances the view of your plant - meeting the diverse needs of operations, maintenance and plant management. The simple to use display structure provides data to users in a fast and meaningful way.

- Meets requirement for 21 CFR Part 11
- Client/server architecture with master/backup servers
- Defined display structure
- Trending
- Sophisticated alarm functionality
- Batch manager to ISA-S88
- Single global database
- Time Synchronisation

Information Manager

The Information Manager combines the power and flexibility of a relational database with the speed and compression of a real time historian package.

- Capture and stores all plant data
- Real-time and historical plant information accessible to the entire organisation
- Embedded Microsoft SQL Server provides standard access via SQL queries
- Based on Wonderware's IndustrialSQL Server™ real-time plant historian
- 21 CFR Part 11 Validatable
- Client Server architecture

Advanced DCS Controller Range

Eurotherm T Series configurable controllers offer the strategy elements of DCS systems capable of continuous analogue, logic and sequential control. They may be used stand alone or as building blocks for larger systems.

- Distributed control units
- Full function continuous and sequential control
- Optional redundancy with bumpless transfer and live replacement
- Unit supervisor concept in line with ISA-S88 Batch Model Control
- Peer-to-peer communication
- Support for Modbus network master and slave
- Support for Profibus network master

Discrete Controller Range

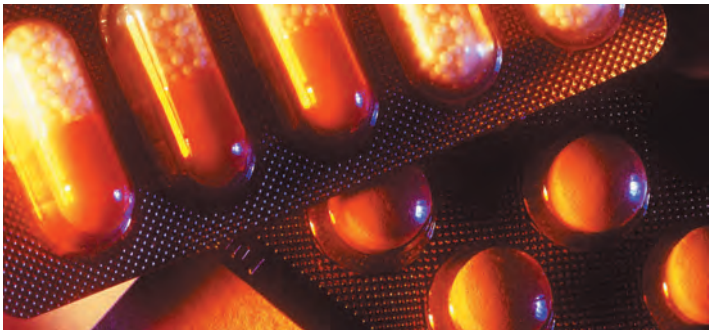
With over 15 models, the 2000 and 3000 Series controllers and indicators are available from a single loop controller for small applications to multi-loop controllers with logic capability for more complex applications.

- One to multi PID loops
- Maths functions
- Logic functions
- Automatic PID tuning
- Support for Profibus, Modbus, DeviceNet networks
- Lockout front panel keys for use with 21 CFR Part 11 operator display
- Switchover of inputs upon failure

Eycon™ Visual Supervisor

The Eycon Visual Supervisor is a multi-function controller with data logging and integrated display – providing all of the features required to control and monitor processes. It can be used as a stand-alone or as a building block within a larger system.

- Meets requirement of 21 CFR Part 11 for Electronic Records and Electronic Signatures
- Batch manager to ISA-S88 with batch log
- Recipe and setpoint programmer
- Accurate continuous and sequential control
- Support for Modbus and Profibus networks
- Barcode reader & printer support
- Time Synchronisation
- Support for USB



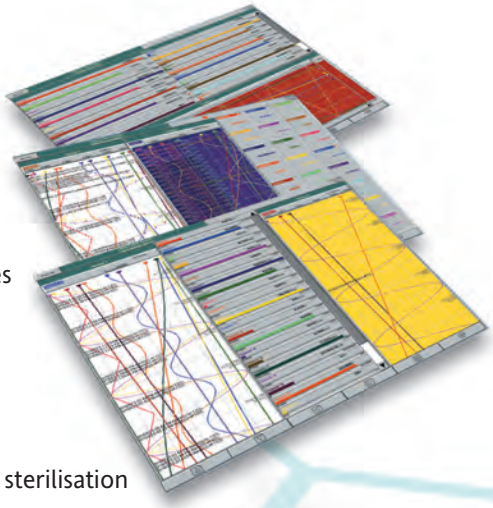
Eurotherm products: The most complete set of products for Life Sciences solutions from a single supplier

Data Management

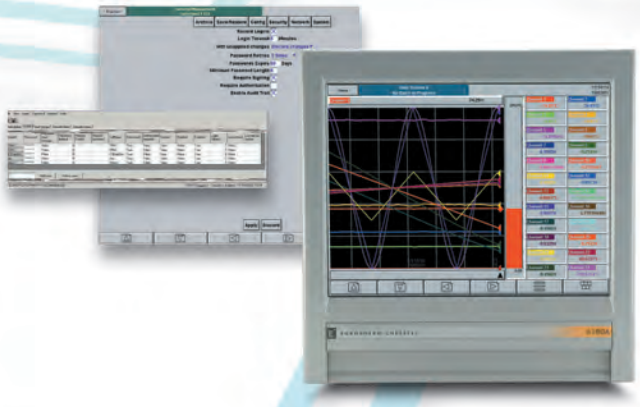
Eurotherm provides a complete range of products from strip and circular paper chart recorders to graphic recorders to networked, plant wide Data Management solutions.

Electronic Data Recording

Products are designed to acquire process data and then to display, transfer and manage that data using secure yet flexible means to meet varying user needs.



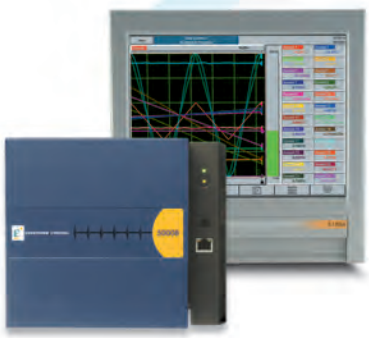
- Meets requirements of 21 CFR Part 11 for Electronic Records and Electronic Signatures
- Multi-batch recording
- Range of Ethernet protocols available
- Standard networking via Ethernet
- Maths capability including Mean Kinetic Temperature calculation, F0 calculation for sterilisation
- Remote viewing via Bridge software
- Time Synchronisation
- Offline data viewing via Review software
- Report generation
- Direct printer output
- Support for Email/SMS notification
- Web visualisation



Paper Recorders

Eurotherm offers a versatile range of strip and circular chart recorders. The 4000 Series is a 100mm strip and the 392/394 in 10” circular chart size.

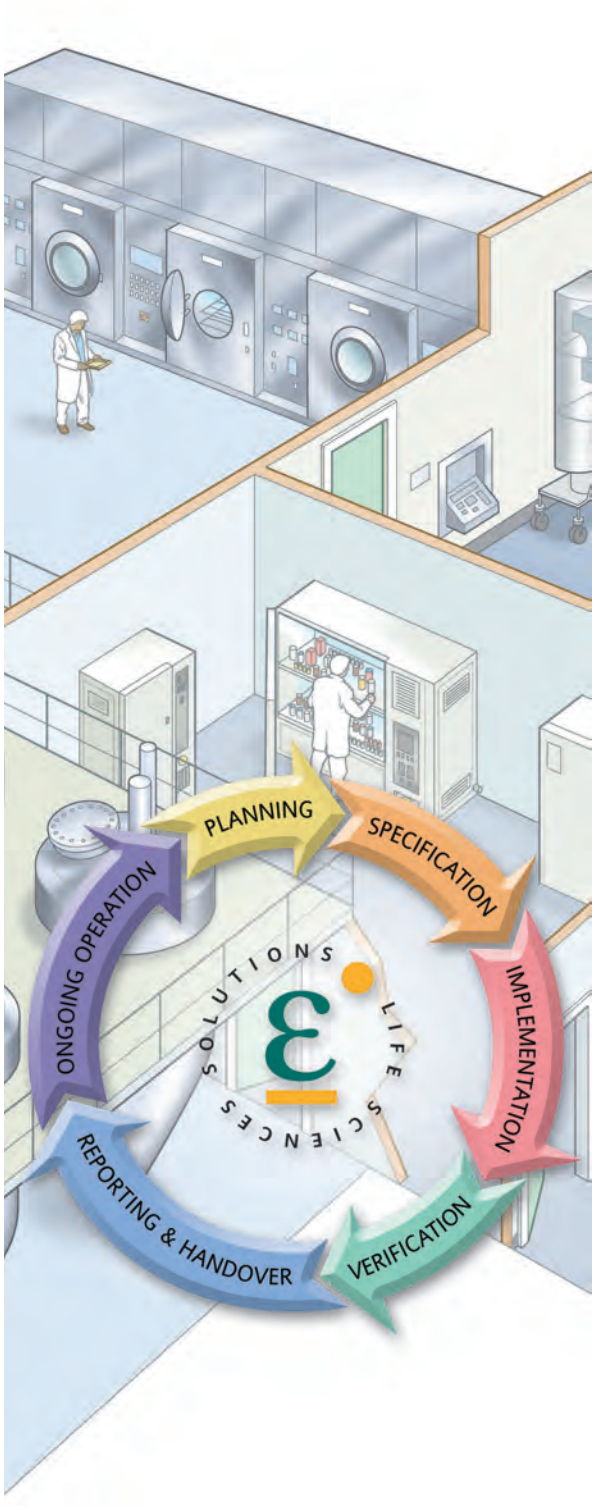
These ranges of paper chart recorders offer a wide range of features that include: annotation, custom messages, powerful maths pack and local archiving to PC card.



- Up to 48 universal inputs
- Remote chart control
- Analogue retransmission
- Maths pack including F0 calculation for sterilisation
- Offline data viewing via Review software
- Online configuration
- Serial communications
- Pen offset compensation

Life Sciences CATALOGUE

APPLICATION NOTES



- The Freeze Drying Process
- The Fermentation Process
- The Tablet Coating Process
- The Water Purification Process
- The Hydrogenation Process
- The Sterilisation Process (Autoclaves)
- Ethylene Oxide (EtO) Sterilisation Process
- The Spray Drying Process
- Pharmaceutical Environmental and Stability Chamber monitoring
- Environmental Monitoring System
- pH Control
- Burner Combustion Control for Boilers
- Pump Sequence Control
- Boiler Drum Level Control
- Boiler Blowdown Control
- Duty/Standby Control Module
- Demand Load Management
- Make-up Water Control
- Building Management Systems & Environmental Monitoring Systems (BMS & EMS)
- Environmental Quality Monitoring Systems

- Control and sequencing
- Recipes
- Batch control & reporting
- Setpoint programming
- Bespoke displays
- Alarm management
- 21 CFR Part 11

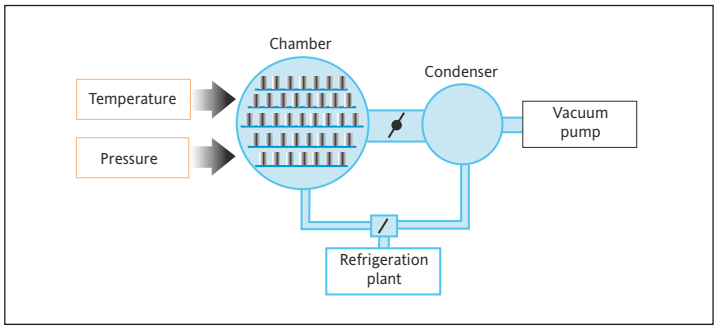
The Freeze Drying process
Application Note

Freeze drying is a slow batch process used in pharmaceutical & biochemical industries to extract dry product from an aqueous solution. The product is usually in phials placed on shelves in a vacuum chamber, which is first frozen and then evacuated. The shelves are then warmed up very slowly, boiling off the liquid, whilst the chamber is continuously evacuated through a cold condenser. Once above zero degrees the chamber isolation valve is closed and a 'Pressure Rise Test' is performed to ensure the product is dry.

Because of the high value of the product even automated freeze dryers go to wait states where the operator validates the readiness of the process to move on to the next stage.

Design & Control

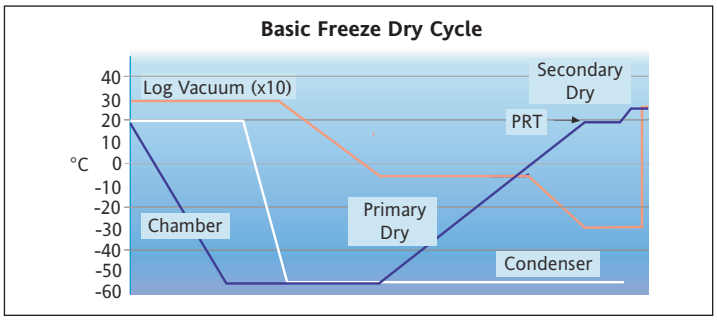
There are many different arrangements for freeze dryers but the basics are outlined here.



Temperature can either be controlled electrically using heating mats on the shelves, or by circulating oil through pipes welded to the shelves in the chamber. The temperature of the chamber, shelves (and/or heating oil), plus condenser form part of the control and monitoring variables.

The vacuum pressure is measured with a Pirani gauge. Control is achieved either by an analogue needle valve or coarse and fine admittance valves. A change over valve is used to switch the refrigeration plant from freezing the chamber to freezing the condenser. In the final drying stage, the condenser, by then full of ice, may be isolated.

The freeze drying process is characterised by long stabilisation periods, for example when the chamber is first frozen, to ensure all the product is completely frozen before the chamber evacuation starts. This is a typical situation where the operator may be required to visually check and confirm that the product and plant are ready for the evacuation to proceed.



The critical phase is the heating phase where the rate at which the water boils off must be slow enough not to damage the product. During this phase, the vacuum is held constant to give consistent conditions. The temperature ramp has to be held if the vacuum rises too much, indicating that the water is coming off too fast.

At the end of the Primary Drying heat ramp, a Pressure Rise Test (PRT) is performed. Here the chamber isolation valve is closed for a defined period - if the product is dry the vacuum is maintained, if the pressure rises more than a nominal amount the product is not completely dry. In this case, the isolation valve is then reopened for another period before a second test is performed.

After the PRT, Secondary Drying takes place to ensure absolute dryness. The product is brought up to or just above ambient temperature.

The plant usually requires sterilisation. This is achieved by an alternative strategy within the control system.

A control system must therefore provide excellent HMI and flexibility, in addition to accurate and reliable control of each freeze drying cycle. It will include the following features:

- Precise temperature control with ramping
- Sequential control of the temperature, vacuum and the refrigeration plant, both for freeze drying and sterilisation
- Safety strategies to ensure product is not damaged as a result of plant failure
- Clear indications to the local operator of key process parameters and states
- Collection of data for analysis and evidence

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for autoclave applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Freeze drying plants are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameters
- Electronic signature

21 CFR Part 11
ENHANCED FOR

With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Freeze dryer temperature and pressure, condenser temperature, pumps RPM
Analogue outputs	Water, steam and nitrogen control, control valves, heater, vacuum retransmission
Digital inputs	Valve limit switches, pump status
Digital outputs	Valve control solenoids, vacuum and circulation pump controls

System building blocks:

- Single freeze dryer (single Eycon visual supervisor)
- Multiple units with supervisory workstation(s)

- **Control and sequencing**
- **Recipes**
- **Batch control & reporting**
- **Setpoint programming**
- **Bespoke displays**
- **Alarm management**
- **21 CFR Part 11**

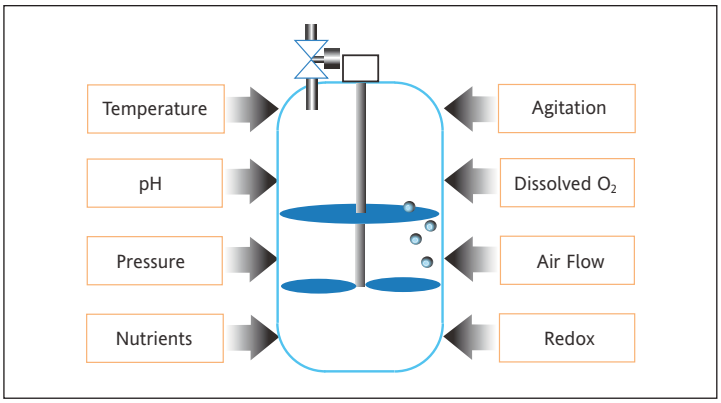
The Fermentation Process
Application Note

Fermentation is widely used within the Pharmaceutical and Food industries. It requires the cultivation in submerged culture of an identified micro-organism (mainly bacterial) as a monoculture under defined environmental conditions. The incubation regime imposed is designed to maximise the productivity of the organism of interest by providing optimal conditions for population growth (biomass). The product of interest might be a bioactive metabolite or recombinant protein.

During an incubation cycle a nutrient energy source (e.g. glucose) is added and the biomass and end product will increase as this is depleted.

Fermenter Design & Control

Incubation control necessitates the precise control of a number of parameters. Of primary importance are:



Temperature, pH, DO_2 or Redox, agitation, pressure, foam control, auxiliary feed or a combination of these controllers.

The control of these and any other parameters is most usually carried out in fermenter vessels specifically designed for the purpose and accommodating various working volumes depending on the yield and production requirements. Laboratory scale vessels could have a capacity of just 10 litres or less whereas production vessels may be as large as several thousand litres.

The smallest units may incorporate an electrical heater and feed stocks (e.g. Nutrient and pH control agents) may be fed from flasks via peristaltic pumps. Larger vessels have an integral jacket for controlling temperature via hot or cold water and allowing indirect sterilisation using injected steam. Where larger quantities of feed stock are required they may be held in separate pressurised tanks and fed via a 'thrust pump' arrangement of valves.

The actual fermentation process is known as the Incubation Phase and is just part of the batch cycle. A complete fermentation cycle can typically include the following steps (depending on vessel design):

- Empty (Blank) Sterilisation of vessel & pipework using direct Steam Injection
- Charging with base medium
- Indirect Sterilisation via Steam Injected into the vessel jacket
- Cooling & Jacket Drain
- Pre-Inoculation – Vessel environment under control

- Inoculation – Injection of a small sample of the monoculture
- Incubation – The Fermentation process itself
- Harvesting – Product removed ready for extraction processes

The R&D and Clinical Trials environments in which many small scale fermenters operate are such that it is not possible to predict the nature of any particular fermentation process either in terms of culture or incubation conditions. Production facilities must also cater for a variety of products each having precisely defined incubation profiles.

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the fermentation environment is achieved and will include the following features:

- Precise loop control with setpoint profile programming
- Recipe Management System for easy parameterisation
- Sequential control for vessel sterilisation and more complex control strategies
- Secure collection of on-line data from the fermenter system for analysis and evidence
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for fermentation applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

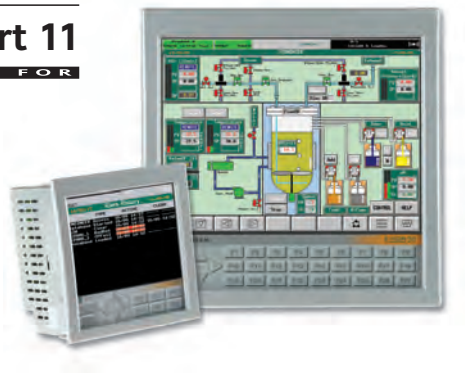
21 CFR Part 11 - 'Ready to use!'

Fermentation plants are in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameter
- Electronic signature

21 CFR Part 11
ENHANCED FOR



With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Temperature, pressure, RPM, VVM and probes for pH, DO2 etc. Additional measurements: Weight, CO2 etc.
Analogue outputs	Water/Steam control valves, Air Flow/Pressure regulators
Digital inputs	Foam detection, high level limit, bursting disc
Digital outputs	Valve control solenoids, pump control etc.

System building blocks:

- Single fermenter (single Eycon visual supervisor)
- Fermenter group (most Eycon visual supervisor functions support up to 4 independent fermenter units)
- Multiple units with supervisory workstation(s)

- **Control and sequencing**
- **Recipes**
- **Batch control & reporting**
- **Setpoint programming**
- **Bespoke displays**
- **Alarm management**
- **21 CFR Part 11**

The Tablet Coating Process
Application Note

Many solid pharmaceutical dosage mediums are produced with coatings, either on the external surface of tablets, or on materials dispensed within gelatine capsules. Coating serves a number of purposes:

- Protects the tablet (or the capsule contents) from stomach acids
- Protects the stomach lining from aggressive drugs such as enteric-coated aspirin
- Provides a delayed release of the medication
- Helps maintain the shape of the tablet

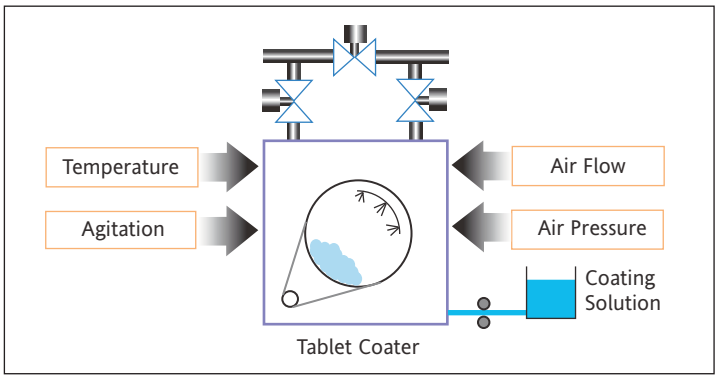
Ideally, the tablet should release the material gradually and the drug should be available for digestion beyond the stomach. The coating can be specially formulated to regulate how fast the tablet dissolves and where the active drugs are to be absorbed into the body after ingestion.

Many factors can affect the end-use properties of pharmaceutical tablets:

- Chemical composition
- Coating process
- Drying time
- Storage and environmental monitoring

Coating Process Design & Control

Tablet coating takes place in a controlled atmosphere inside a perforated rotating drum. Angled baffles fitted into the drum and air flow inside the drum provide means of mixing the tablet bed. As a result, the tablets are lifted and turned from the sides into the centre of the drum, exposing each tablet surface to an even amount of deposited/sprayed coating.



Tablet Coater

The liquid spray coating is then dried onto the tablets by heated air drawn through the tablet bed from an inlet fan. The air flow is regulated for temperature and volume to provide controlled drying and extracting rates, and at the same time, maintaining the drum pressure slightly negative relative to the room in order to provide a completely isolated process atmosphere for the operator.
Tablet coating equipment may include spray guns, coating pan, polishing pans, solution tanks, blenders and mixers, homogenisers, mills, peristaltic pumps, fans, steam jackets, exhaust and heating pipes, scales and filters.
Tablet coating processes may include sugar coating (any mixtures of purified water, cellulose derivatives, polyvinyl, gums and sugar) or film coating (purified water, cellulose derivatives).

The coating process is usually a batch driven task consisting of the following phases:

- Batch identification and Recipe selection (film or sugar coating)
- Loading/Dispensing (accurate dosing of all required raw materials)
- Warming
- Spraying (application and rolling are carried out simultaneously)
- Drying
- Cooling
- Unloading

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the coating environment is achieved and will include the following features:

- Precise loop control with setpoint profile programming
- Recipe Management System for easy parameterisation
- Sequential control for complex control strategies
- Secure collection of on-line data from the coating system for analysis and evidence
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for autoclave applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Tablet coating machines are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameters
- Electronic signature

21 CFR Part 11
ENHANCED FOR

With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Temperatures (inlet and outlet air), air flow, differential pressure (Pan), pressure (atomising air), RPM, level, etc.
Analogue outputs	Control valves, air flow/pressure regulators, fans and pumps speeds
Digital inputs	Coating solution low level switch, fans and pumps statuses, etc.
Digital outputs	Valve control solenoids, pump control etc.

System building blocks:

- Single coating unit (single Eycon visual supervisor)
- Multiple units with supervisory workstation(s)

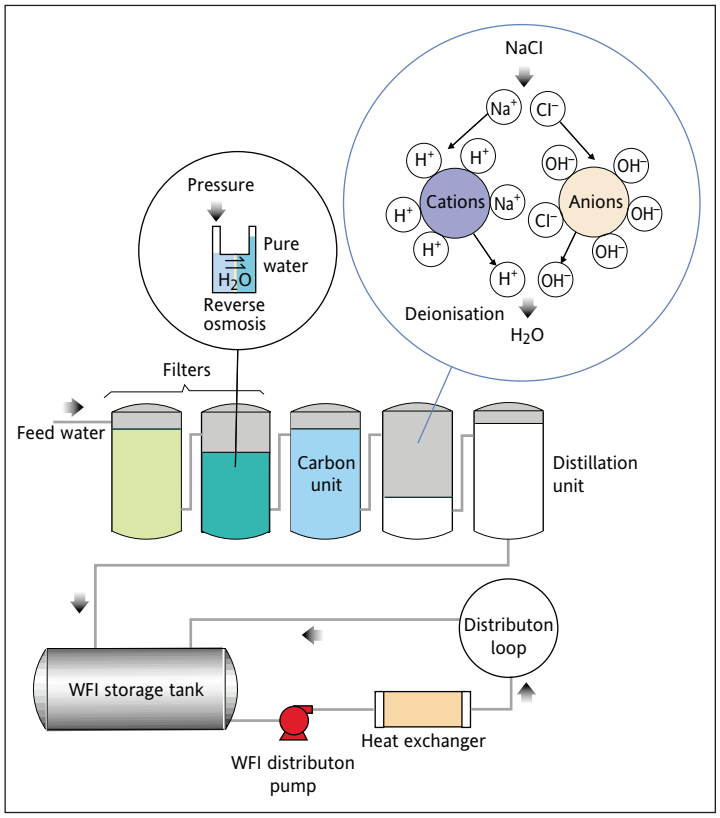
- Control and sequencing
- Recipes
- Batch control & reporting
- Setpoint programming
- Bespoke displays
- Alarm management
- 21 CFR Part 11

The Water Purification Process

Application Note

Water purity is extremely important to pharmaceutical and biochemical industries. Suspended or dissolved particles, organic compounds, impurities and other contaminants prohibit the usage of tap water in laboratory applications and scientific research.

Parameters such as resistivity, conductivity, size of particulate matter and concentration of micro-organisms are used to categorise water quality and, therefore, specify intended uses for water. Some applications can tolerate the presence of specific impurities in the water, but others, such as High Performance Liquid Chromatography (HPLC) require removal of the majority of contaminants.



Contaminants

Water is an excellent solvent and can be sourced from almost anywhere on Earth. This property makes it prone to all kinds of contamination.

- Particulates: Silt and debris which can be removed by passing water through a 10 to 20 micron filter (or less if necessary).
- Micro-organisms: Bacterial agents constitute a real challenge for water purification systems. Their growth rate, size and robustness require an efficient design (detection, removal from water inlet, inhibition of growth, etc.). Bacteria are measured in colony forming units per millilitre and can be killed with disinfectants. As a result, their secretions and cellular fragments must also be removed to avoid contamination.
- Endotoxins, pyrogens, DNA and RNA: Cellular fragments and bacterial by-products. Harmful to tissue cultures. Can be detected with a Limus Amoebocyte Lysate (LAL) test.

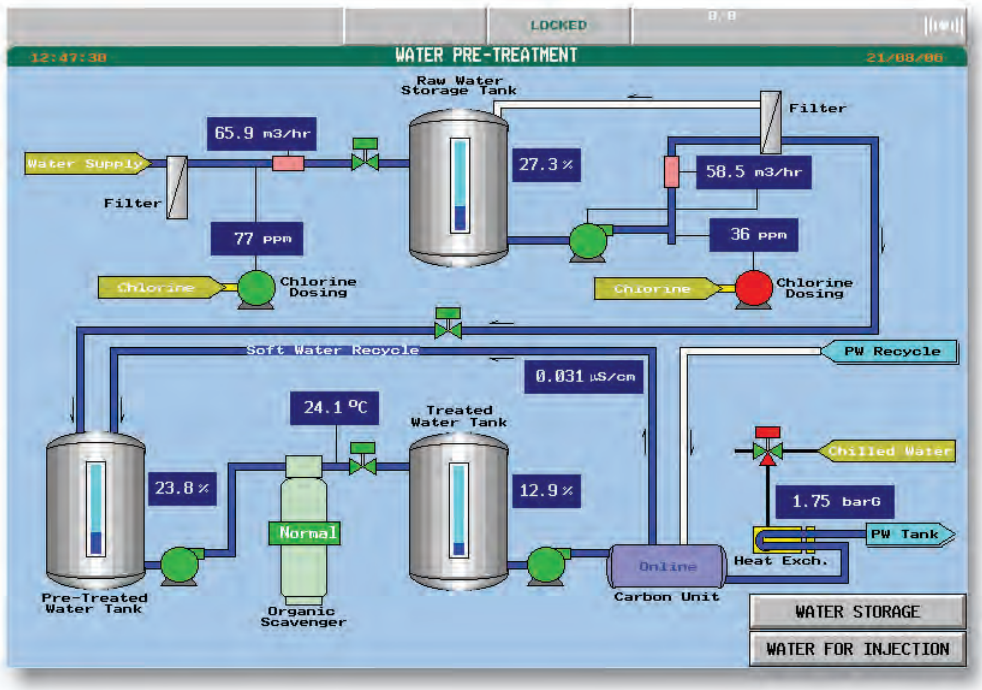
- Dissolved inorganic elements: Include phosphates, nitrates, calcium and magnesium, carbon dioxide, silicates, iron, chloride, fluoride, and any other natural or man-made chemicals resulting from exposure to the environment. Electrical conductivity (µSiemens/cm) is used to monitor high concentration of ions, while resistivity (MΩcm) is used to identify ions if present in small concentrations. These contaminants affect water hardness and alkalinity/acidity.
- Dissolved organic elements: Pesticides, plant and animal remains or fragments. Total Organic Carbon (TOC) analysers are used to measure CO2 emitted by organics subjected to oxidisation. Organic-free water is mainly used in applications where analysis of organic substances is carried out (e.g. HPLC, chromatography and mass spectrometry).

Scientific applications require elimination of certain types of contaminants. On the other hand, pharmaceutical productions require, in most cases, near-total removal of impurities (criteria dictated by specific standards or local/international regulatory bodies).

Purification Process

There are a number of methods commonly used to purify water. Their effectiveness is linked to the type of contaminant being treated and the type of application the water will be used for.

- Filtration: This process can take the form of any of the following:
  - Coarse filtration: Also called particle filtration, it can utilise anything from a 1 mm sand filter, to a 1 micron cartridge filter.
  - Microfiltration: Uses 1 to 0.1 micron devices to filter out bacteria. A typical implementation of this technique can be found in the brewing process.
  - Ultrafiltration: Removes pyrogens, endotoxins, DNA and RNA fragments.
  - Reverse osmosis: Often referred to as RO, reverse osmosis is the most refined degree of liquid filtration. Instead of a filter, it uses a porous material acting as a unidirectional sieve that can separate molecular-sized particles.
- Distillation: Oldest method of purification. Inexpensive but cannot be used for an on-demand process. Water must be distilled and then stored for later use, making it again prone to contamination if not stored properly.
- Activated carbon adsorption: Operates like a magnet on chlorine and organic compounds.
- Ultraviolet radiation: At a certain wavelength, this might cause bacteria to be sterilised and other micro organics to be broken down.
- Deionisation: Also known as ion exchange, it is used for producing purified water on-demand, by passing water through resin beds. Negatively charged (cationic) resin removes positive ions, while positively charged one (anionic) removes negative ions. Continuous monitoring and maintenance of the cartridges can produce the purest water.



Hot Water Sanitisation

Sanitisation of water purification equipment with hot water is achieved via an appropriate combination of exposure time and temperature. A primary use for this process is to deactivate viable microbes. It is worth mentioning that Endotoxin reduction is not achieved as a direct result of the hot water sanitisation process.

Based on the feed water source, system operating conditions and the end-user's operating and maintenance procedures, traditional chemical cleaning processes may still be required.

Sanitisation using hot water involves incorporating heat exchangers into the traditional clean in place (CIP) system to gradually heat and cool water circulating through the reverse osmosis membrane system. Membrane manufacturers commonly stipulate a controlled heating and cooling rate to protect against irreversible damage to the membrane and ensure the system's long-term performance.

A typical hot water sanitisation sequence would consist of the following phases:

- Initialisation (conditions checking)
- Heating
- Holding
- Cooling

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the sterilisation is achieved and will include the following features:

- Precise loop control with setpoint profile programming
- Sequential control for sanitation/sterilisation
- Onscreen operator messaging
- Duty standby pump control
- Secure collection of on-line data from the purified water system for analysis and evidence
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for autoclave applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Water purification plants are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameter
- Electronic signature

21 CFR Part 11
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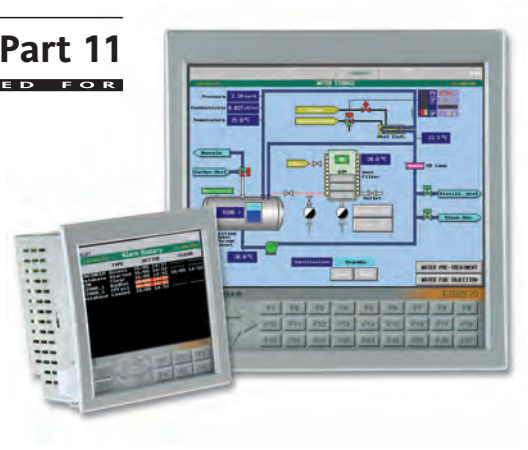


With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Temperature, water flow, line pressures, level, pH, conductivity, chlorine and carbon measurements, etc.
Analogue outputs	Control valves, flow/pressure regulators, pumps speed
Digital inputs	Bursting discs, conductivity and other analytical measurements alarms, valves and pumps statues, etc.
Digital outputs	Valve control solenoids, pump control etc.

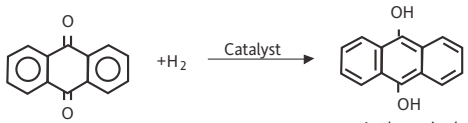
System building blocks:

- Pre-treated water system (single Eycon visual supervisor)
- Water for injection and distribution system (single Eycon visual supervisor)
- Complete system with supervisory workstation(s)

- **Control and sequencing**
- **Recipes**
- **Batch control & reporting**
- **Setpoint programming**
- **Bespoke displays**
- **Alarm management**
- **21 CFR Part 11**

The Hydrogenation Process
Application Note

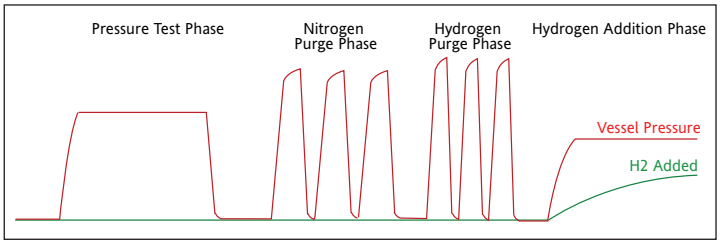
Hydrogenation is the chemical addition of hydrogen to a hydrocarbon in the presence of a catalyst, a severe form of hydrogen treating. Hydrogenation may be either destructive or non-destructive. In the former case, hydrocarbon chains are ruptured (cracked) and hydrogen is added where the breaks have occurred. In the latter, hydrogen is added to a molecule that is unsaturated with respect to hydrogen. In either case, the resulting molecules are highly stable.



Anthraquinone *Anthraquinol*

Hydrogenator Design and Control

The use of hydrogen requires precautions against creating an explosive mix of hydrogen and air. Typically, a hydrogenation vessel undergoes a pressure test followed by several nitrogen purges before hydrogen is introduced. Similarly, at the end of the reaction process, the vessel is purged with nitrogen in order to leave it in a safe condition. Normally, a hardwired safety system confirms the pressure test and nitrogen purge phases before allowing the hydrogen line to be opened.



Hydrogenation requires high pressures to be maintained in the reaction vessel - giving problems over maintaining seals around agitators which in some cases require additional seal integrity checks or upgrades to incorporate magnetic coupling systems.

Hydrogenation also tends to be a highly exothermic reaction, resulting in demanding temperature control requirements.

The R&D and Clinical Trials environments in which many small scale hydrogenation vessels operate are such that facilities must cater for a variety of products each having precisely defined requirements both for the hydrogen addition itself and for the associated temperature profile.

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the hydrogenation environment is achieved and will include the following features:

- Sequential control for vessel pressure testing, purging and hydrogen addition.
- Precise loop control for temperature and pressure (temperature setpoint profile programming is also available on the Eycon™ Visual Supervisor if required).
- Secure collection of on-line data from the hydrogenation process for analysis and evidence.
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for hydrogenation applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Many hydrogenation vessels are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameter
- Electronic signature

21 CFR Part 11
ENHANCED FOR

With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Temperature, pressure, RPM
Analogue outputs	Pressure control valves, heaters, cooling fluid control valves
Digital inputs	Seal status, bursting disk, valve status feedback, handshaking with hardwired safety system
Digital outputs	Valve control solenoids, pump control, handshaking with hardwired safety system

System building blocks:

- Single hydrogenation vessel (single Eycon visual supervisor)
- Multiple units with supervisory workstation(s)

- **Control and sequencing**
- **Recipes**
- **Batch control & reporting**
- **Setpoint programming**
- **Bespoke displays**
- **Alarm management**
- **21 CFR Part 11**

The Sterilisation Process (Autoclave)

Application Note

Through history, humans have used fire to purify items. Heat generated through application of high temperatures acts by disrupting membranes and denaturing proteins and nucleic acids. Burning, however, is a bit excessive for everyday usage.

Transmissible agents (such as spores, bacteria and viruses) can be eliminated through sterilisation. This is different from disinfection, where only organisms that can cause disease are removed.

Some of the methods used to achieve sterilisation are:

- Autoclaves: Highly effective and inexpensive. Unsuitable for heat sensitive objects.
- Hot air ovens: Inefficient compared to autoclaves.
- Ethylene oxide: Suitable for heat sensitive items but leaves toxic residue on sterilised items.
- Low-temperature steam and formaldehyde: Effective for instruments with cavities or tubular openings.
- Sporicidal chemicals: Often used as disinfectants but can also sterilise instruments if used for prolonged periods.
- Irradiation: Gamma rays and accelerated electrons are excellent at sterilisation.
- Gas plasma.

The preferred principle for sterilisation is through heat, the autoclave being the most widely used method of achieving it.

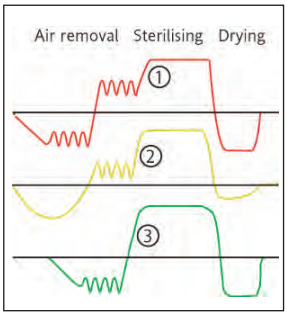
In a dry air oven, it takes two hours at 160°C to kill spores of the bacterium Clostridium botulinium (associated with canned food). Using saturated steam, the same spores are killed in just five minutes at 121°C, proving that moist heat is more effective than dry heat.

Autoclave Design and Control

To be effective against spore forming bacteria and viruses, autoclaves need to:

- Have steam in direct contact with the material being sterilised (i.e. loading of items is very important).
- Create vacuum in order to displace all the air initially present in the autoclave and replacing it with steam.
- Implement a well designed control scheme for steam evacuation and cooling so that the load does not perish.

The efficiency of the sterilisation process depends on two major factors. One of them is the thermal death time, i.e. the time microbes must be exposed to at a particular temperature before they are all dead. The second factor is the thermal death point or temperature at which all microbes in a sample are killed.



The steam and pressure ensure sufficient heat is transferred into the organism to kill them. A series of negative pressure pulses are used to vacuum all possible air pockets, while steam penetration is maximised by application of a succession of positive pulses.

Typical pressure cycles used in autoclaves are:

1. Cycle for fabrics, assembled filter units and discard loads.
2. Cycle for laboratory plastic and glassware.
3. Cycle mainly used for discard loads.

Process performance can be confirmed by monitoring colour changes on indicator tape often taped onto packages or products to be autoclaved. Biological indicators such as the Attests can also be used. These contain Bacillus sterothermophilus spores, which are amongst the toughest organisms an autoclave will have to destroy. After a run in an autoclave, the internal glass in the Attest vial is shattered, allowing the spores into a differential liquid medium. If the autoclave has destroyed the spores, the medium remains a blue colour. Otherwise, the spores will metabolise, causing a yellow colour change after two days of incubation at 56°C.

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the sterilisation is achieved and will include the following features:

- Precise loop control with setpoint profile programming
- Recipe Management System for easy parameterisation
- Sequential control for complex control strategies
- Secure collection of on-line data from the sterilisation system for analysis and evidence
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for autoclave applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Autoclaves are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

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21 CFR Part 11
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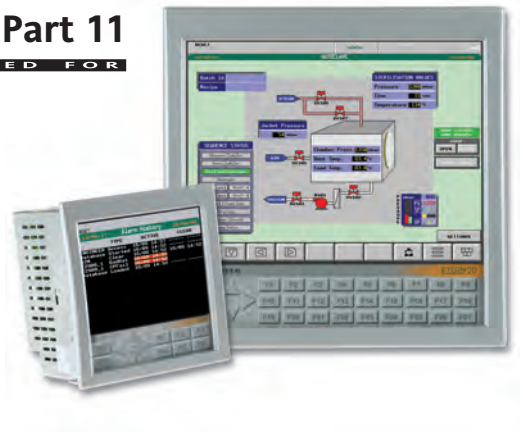


With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Jacket, chamber, drain, load probe, air detector and air filter temperatures, jacket and chamber pressures
Analogue outputs	Steam control valve, pressure regulator
Digital inputs	Door closed, locked, sealed; switches, emergency stop
Digital outputs	Valve control solenoids, pump/fan controls

System building blocks:

- Autoclave (single Eycon visual supervisor)
- Multiple autoclaves with supervisory workstation(s)

INDUSTRY

- **Recipe downloads**
- **Safety interlocks**
- **Autobatch release**
- **Temperature control**
- **Vacuum control**
- **21 CFR Part 11**

Ethylene Oxide (EtO) Sterilisation Process

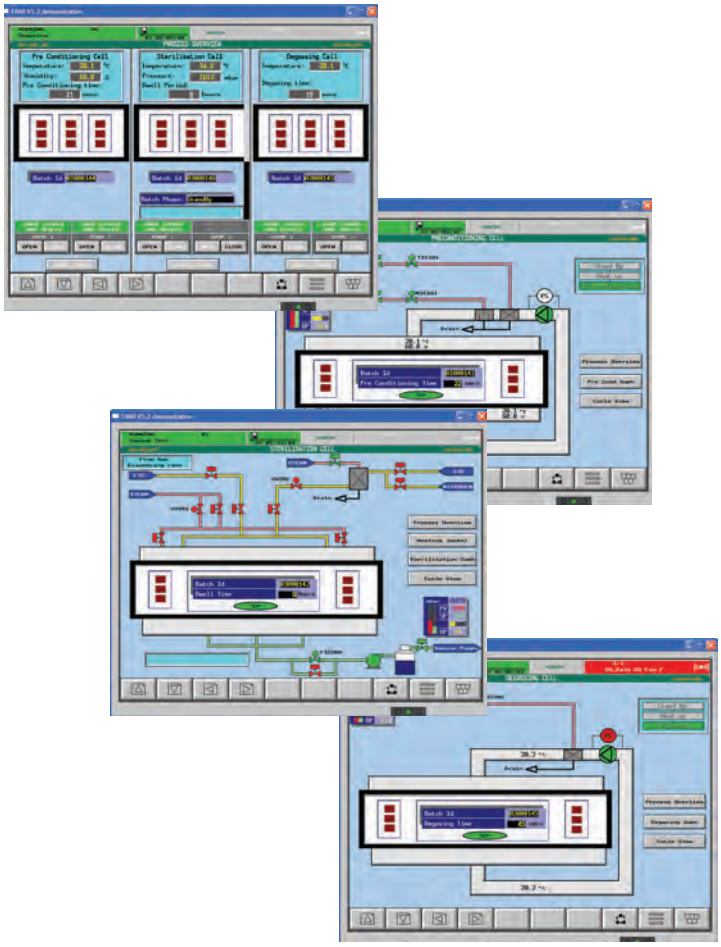
Application Note

Ethylene Oxide (EtO) sterilisation is mainly used to sterilise medical and pharmaceutical products that cannot support conventional high temperature steam sterilisation - such as devices that incorporate electronic components, plastic packaging or plastic containers.

EtO gas infiltrates packages as well as products themselves to kill micro organisms that are left during production or packaging processes. This gas, mixed with air at a ratio of at least 3% EtO gas, forms an explosive mixture. Pure EtO gas boiling point is 10.73 °C at atmospheric pressure. Most of the time, it is mixed with Nitrogen or CO2. This explosive condition requires Intrinsic Safe material (ATEX) zoning, for security of people as well as security of the process itself.

Safety of personnel is an important issue due to the harmful effect of EtO on humans. Polluted areas need to be alarmed using gas detectors set up at different locations to monitor any leak. Visual and audio alarm systems need to be provided. The system must inform any operator when a sterilisation cell contains EtO.

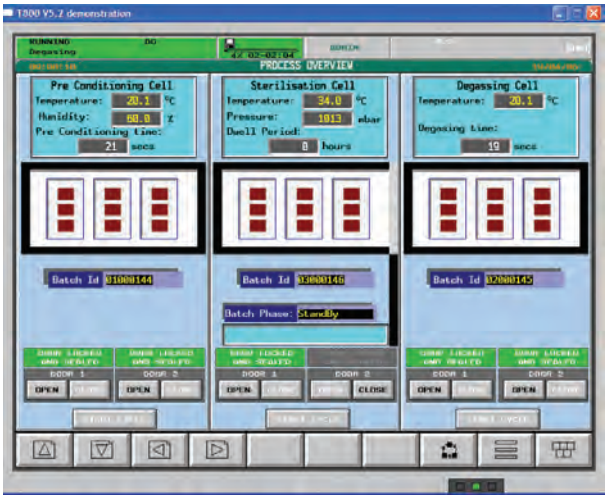
When this toxic gas is removed from the room it needs to be treated using thermal burners, scrubbers or oxidation for environmental protection or be transported to an alternate facility for treatment.



EtO Sterilisation process:

Most EtO sterilisation lines involve three different stages. These can be separated into three different cells depending on the size or amount of devices to treat:

- **PRE CONDITIONING**
- **STERILISER**
- **DEGASSER**

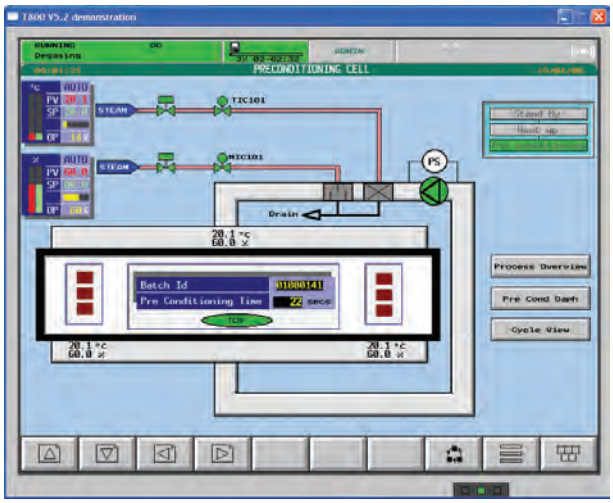


When cells are separated, automated loading/unloading systems are required. These save operator time as well as giving protection from exposure to a polluted environment, which could be detrimental to health.

PRE CONDITIONING STAGE

First, products need to go through a pre conditioning phase to make micro organisms grow. The batch load goes through a dwell time under a controlled environment of:

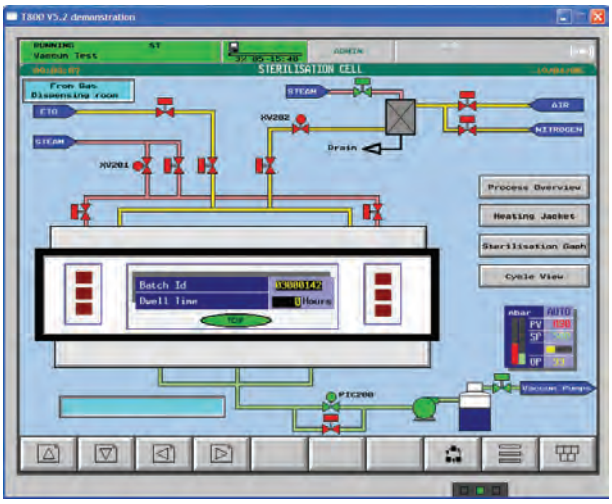
- **Temperature**
- **Humidity**



STERILISER STAGE

Then the load goes through a long and complex sterilisation cycle. Requirements of such a system are:

- **Accurate temperature control**
- **Availability of the control system**
- **Accurate pressure and vacuum control**
- **Easy displays of process phases**
- **Dedicated customer recipes**
- **Auto batching release through tolerance tests**
- **Reporting**
- **Security interlocks between actuators**
- **Alarming**
- **Shut down strategies**
- **Audit Trail facilities – Trending**
- **21CFR Part11**



During this cycle, accurate temperature control is important and a heating jacket is used. As the overall duration of this cycle is around 60 hours, high availability of the system is vital and system redundancy is required. Doubling sensors, actuators and controllers as well as changeover facilities on these components, helps to ensure the product is sterilised even on hardware or software failure.

After the doors have been shut down and sealed correctly, the cycle can be started either manually or automatically. If any problem with door sealing is detected the cycle is interlocked and cannot start. Security interlocks are also used between air and EtO valves.

Once the cycle is started, easy to use displays are required to show:

- **The actual phase of sterilisation**
- **All the key set points and tolerances as loaded by the recipe**
- **All the key process values for the auto batch release facility**

Control of vacuum and pressure is also required. Due to the toxic effect of EtO, water ring rotary pumps are used. The vacuum process needs to perform the emergency evacuation phase for a fast evacuation of gas.

The sterilisation phases are:

- **Cycle start delay to enable the system to start in stable conditions**
- **General cell temperature check**
- **Initial vacuum phase**
- **Leak rate test**
- **First flush**
- **Second flush**
- **DEC (Dynamic Environmental Conditioning)**
- **EtO gas injection**
- **Sterilisation dwell time period under EtO**
- **Post dwell vacuum level**
- **First wash**
- **Second wash**
- **Final air admission**
- **Final chamber re-evacuation delay**

During execution of these phases a batch report is generated. This report will include: tolerance checks, phase changes, alarms, events and critical process values. A key feature of the system is “auto batch” release. During the sterilisation cycle if any abnormal condition occurs, the batch will be automatically stopped and condition(s) causing the stoppage will be identified. With this “auto batch” release facility operators do not have to wait until the end of the cycle and spend time going through the batch report to understand why it went wrong. With this feature, provided that batch is completed satisfactory it will be automatically forwarded to the degassing room without human check of tolerance, process values and alarms.

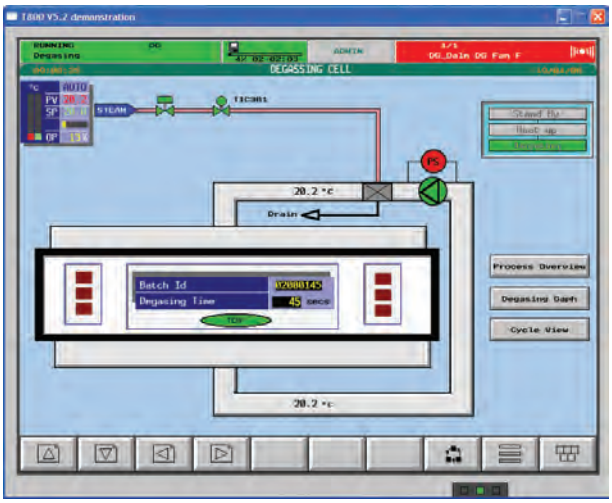
For each batch the operator selects appropriate product recipe. After recipe has been downloaded, the operator is given the opportunity to check if values are correct for this particular batch before starting the cycle.

When the batch is over an automatic print of the report can be performed. Batch logged files are also archived electronically for future review. Batch logged files could be searched by the following:

- **Batch ID**
- **Customer name**
- **Recipe**
- **Product type**
- **Start and stop time**

DEGASSER STAGE

Finally, products need to go through a degassing phase to remove any particle of EtO. The batch load goes over a dwell time under a temperature controlled environment.



Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for EtO steriliser applications because it combines all these key features into a single compact unit:

- **Batch control and reporting**
- **Powerful loop & sequence control**
- **Alarm management**
- **Recipe management**
- **Flexible graphics**
- **Audit trail**
- **SVGA touch screen display IP65**
- **Secure data logging and trending**
- **Access control and electronic signatures**

21 CFR Part 11 Ready

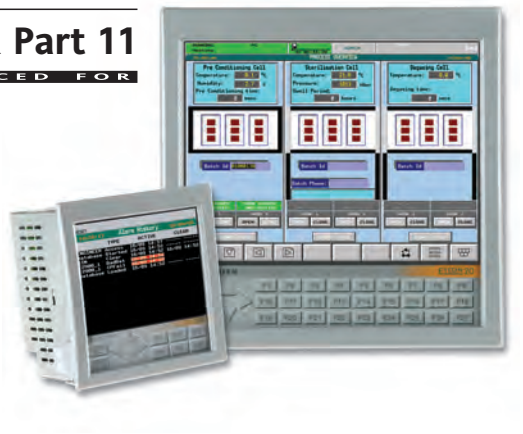
Sterilisation plants are likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The Visual Supervisor has been widely used in validated processes including fermenters, freeze dryers, autoclaves, reactors, purified water systems, tablet coating machines, etc.

The Auditor feature on the Visual Supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameters
- Electronic signature

With the Auditor features, electronic signature is configurable for all actions that may be performed from the Visual Supervisor display including the customised display, standard features such as batch management, recipe changes, access control changes, etc.

21 CFR Part 11
ENHANCED FOR



Scalable architecture:

The Eurotherm Programmable Automation Controller T2550 is ideal for EtO steriliser applications combined with the Eycon visual supervisor, because it offers all these key features:

- **Powerful strategy engine**
- **Multitasking for rapid shutdown strategies**
- **Native redundancy features on critical strategy**
- **Calibration facilities**
- **Powerful loop & sequence control**
- **Scalable by adding slot of I/Os as required**

A range of I/O modules cater for the various interfaces required:

Analogue inputs	Temperature, Humidity, Pressure etc.
Additional measurements	Gas level probes.
Analogue outputs	Steam/Water/Gas control valves, fan speed
Digital inputs	Doors, gas valves and motor status, pallet positions and numbers, etc.
Digital outputs	Valve control solenoids, Pump control, etc.

System building blocks:

- Single steriliser (single Eycon visual supervisor)
- Degassing/Pre-conditioning cells
- Multiple units with supervisory workstations(s)

- **Control and sequencing**
- **Recipes**
- **Batch control & reporting**
- **Setpoint programming**
- **Bespoke displays**
- **Alarm management**
- **21 CFR Part 11**

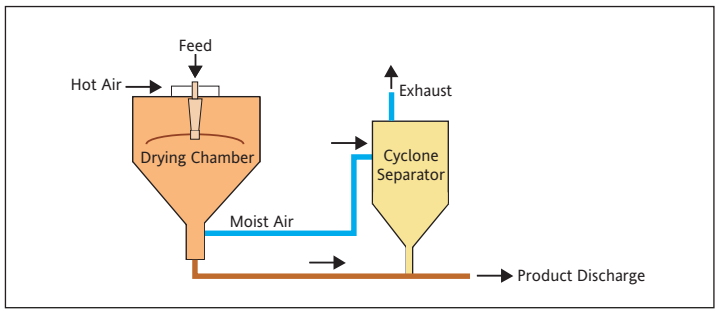
The Spray Drying process
Application Note

The spray drying process is older than might commonly be imagined. Earliest descriptions date from 1860 with the first patented design recorded in 1872. The basic idea of spray drying is the production of highly dispersed powders from a fluid feed by evaporating the solvent. This is achieved by mixing a heated gas with an atomised (sprayed) fluid of high surface-to-mass ratio droplets, ideally of equal size, within a vessel (drying chamber), causing the solvent to evaporate uniformly and quickly through direct contact.

Spray drying can be used in a wide range of applications where the production of a free-flowing powder is required. This method of dehydration has become the most successful one in the following areas:

- Pharmaceuticals
- Bone and tooth amalgams
- Beverages
- Flavours, colourings and plant extracts
- Milk and egg products
- Plastics, polymers and resins
- Soaps and detergents
- Textiles and many more.

Almost all other methods of drying, including use of ovens, freeze dryers or rotary evaporators, produce a mass of material requiring further processing (e.g. grinding and filtering) therefore, producing particles of irregular size and shape. Spray drying on the other hand, offers a very flexible control over powder particle properties such as density, size, flow characteristics and moisture content.



Design and Control

The challenges facing both designers and users are to increase production, improve powder quality and reduce costs. This requires an understanding of the process and a robust control implementation.

Spray drying consists of the following phases:

- Feed preparation: This can be a homogenous, pumpable and free from impurities solution, suspension or paste.
- Atomisation (transforming the feed into droplets): Most critical step in the process. The degree of atomisation controls the drying rate and therefore the dryer size. The most commonly used atomisation techniques are:

1. Pressure nozzle atomisation: Spray created by forcing the fluid through an orifice. This is an energy efficient method which also offers the narrowest particle size distribution.
2. Two-fluid nozzle atomisation: Spray created by mixing the feed with a compressed gas. Least energy efficient method. Useful for making extremely fine particles.
3. Centrifugal atomisation: Spray created by passing the feed through or across a rotating disk. Most resistant to wear and can generally be run for longer periods of time.

- Drying: A constant rate phase ensures moisture evaporates rapidly from the surface of the particle. This is followed by a falling rate period where the drying is controlled by diffusion of water to the surface of the particle.
- Separation of powder from moist gas: To be carried out in an economical (e.g. recycling the drying medium) and pollutant-free manner. Fine particles are generally removed with cyclones, bag filters, precipitators or scrubbers.
- Cooling and packaging.

A control system must therefore provide flexibility in the way in which accurate and repeatable control of the spray drying is achieved and will include the following features:

- Precise loop control with setpoint profile programming
- Recipe Management System for easy parameterisation
- Sequential control for complex control strategies
- Secure collection of on-line data from the system for analysis and evidence
- Local operator display with clear graphics and controlled access to parameters

Eurotherm® Eycon™ Visual Supervisor

The Eurotherm visual supervisor is ideal for autoclave applications because it combines all these key features into a single compact unit:

- **Powerful loop and sequence control**
- **Flexible graphics**
- **Setpoint programmer**
- **Batch control and reporting**
- **Audit trail**
- **XGA touchscreen display to IP65**
- **Secure data logging and trending**
- **Recipe management**
- **Alarm management**
- **Access control and electronic signatures**

21 CFR Part 11 - 'Ready to use!'

Spray drying plants are used in industries likely to require validation to the requirements of the FDA, EMEA or other applicable regulatory body. The visual supervisor has been widely used in validated processes including freeze dryers, autoclaves, reactors, fermenters, purified water systems, tablet coating machines, etc.

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDA's 21 CFR Part 11 including:

- Controlled user access
- Secure data logging in tamper resistant format
- Audit trail recording user actions and changes to process parameters
- Electronic signature

21 CFR Part 11
ENHANCED FOR

With the Auditor feature, Electronic signature is configurable for all actions which may be performed from the visual supervisor display including the customised display and standard features such as batch, recipe changes, access control changes, etc.

Scalable architecture

A complete system can be created in combination with T2550 DIN rail I/O bases. Connection is via ELIN and I/O is scalable by adding 4. 8 or 16 slot bases as required. A range of I/O modules caters for the various interfaces required:

Analogue inputs	Inlet and outlet temperatures, feed pump speed and pressure, air flow rate, particle size, humidity
Analogue outputs	Fan and pump speeds, pressure regulators
Digital inputs	Fan and pump statuses
Digital outputs	Fan and pump controls

System building blocks:

- Spray dryer (single Eycon visual supervisor)
- Multiple units with supervisory workstation(s)

- **Alarm management**
- **21 CFR Part 11**
- **Data storage**
- **Reports**
- **Scalability**

Pharmaceutical Environmental & Stability Chamber Monitoring

Application Note

Monitoring of storage and production environments has become an important issue within the Pharmaceutical Industry. The FDA and other regulatory bodies require not only accurate measurement and storage of room parameters but if the storage medium is electronic then the methods used must comply with 21 CFR Part 11.

Stability Monitoring of medicinal products is an area also addressed by the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and the ICH final guidance (agreed Feb 2003), is now being adopted across Europe, Japan and the United States.

The FDA also states in its 21 CFR part 203 section that manufacturers, authorised distributors of drugs and their representatives shall store and handle all drug samples under conditions that will maintain their stability, integrity and effectiveness, and ensure that the drug samples are free of contamination, deterioration and adulteration.

With environmental chambers, temperature, humidity, particulate counts, differential pressure, lighting, gas levels and other environmental conditions can be controlled. This can be extended to equipment required to detect toxic gases and fume hood positions.

Regulatory bodies require that stability facilities have to meet the following criteria:

- Proper documentation, including SOPs and periodical reports
- Chambers and rooms have to be equipped with multiple sensors spread evenly throughout the controlled area
- Generous multilevel shelving providing orderly storage and proper exposure to the controlled environment
- Acceptable monitoring equipment (probes, recorders, etc.)
- Continuous recording of data and full traceability
- Corrective action taken when stability factors go outside the specifications

Alarms and excursions

Detecting and announcing abnormal conditions is a key requirement for the environmental monitoring systems.

Pharmaceutical companies have adopted various methods for capturing and announcing abnormal conditions. These include:

- Alarms if monitored values go outside a predefined value.
- Alarms on excursion conditions being breached (usually a set temperature or humidity for a particular time).
- Intelligent alarms (e.g. “alarm immediately if it is silent hours, after a period if it is during the day” or “delay the alarm if the room door is known to be open”).
- Alarms based on rolling yearly MKT.
- SMS or e-mail alerts triggered by alarms or events

Mean Kinetic Temperature (MKT)

Measurement and recording of temperatures is vital to the storage of perishable goods, but there is more than one way to record an average.

The ICH defines the mean kinetic temperature as being “a single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period”.

MKT expresses the cumulative thermal stress experienced by a product at varying temperatures, during storage and distribution. It differs from other means (such as a simple numerical average or arithmetic mean) in that higher temperatures are given greater weight in computing the average, thus, recognising the accelerated rate of thermal degradation of materials at higher temperatures.

The mean kinetic temperature is calculated as being:

$$T_k = \frac{\frac{-\Delta H}{R}}{\ln\left[\frac{e^{\frac{-\Delta H}{RT_1}} + \cdots e^{\frac{-\Delta H}{RT_n}}}{n}\right]}$$

T_k being the mean kinetic temperature in Kelvin
ΔH is the heat activation in kjoule per mole
R is the universal gas constant in kjoule per mole per Kelvin
T_1 and T_n are the temperature samples for periods 1 and n, respectively
n is the total number of periods in the calculation

There are a number of interpretations of how this calculation is achieved using real samples:

- All sample values fed into formula
- Maximum/minimum samples fed into formula separately (recommended by the FDA)
- Arithmetic mean of maximum and minimum fed into formula (recommended in the US Pharmacopeia and by the UK MCA)

Eurotherm® offers all the above methods with

- A choice of stability testing period (hourly / daily / weekly)
- A choice of sampling frequency (from 1 minute to 1 hour)
- Option to remove individual probes from calculation (e.g. during a calibration process)
- Corrective action in case stability is out of specification
- Secure and low cost custom reporting
- Significant reduction of the cost of ownership

Eurotherm Scalable and Flexible Solutions

Eurotherm offers a comprehensive range of scalable and flexible solutions which will satisfy the requirements of environmental and stability chamber monitoring for Pharmaceutical and Bio-Pharma industries. These solutions unify the environmental and security data from the manufacturing area for presentation to plant or laboratory managers and operators.

Single room monitoring with 6000 series Data acquisition system

- Meets requirements of 21 CFR part 11
- Single data recorder
- Local storage
- Maths capability including Mean Kinetic Temperature
- Bridge software for remote access and monitoring
- Report software via MS Excel™ Add-in option

Multiple room monitoring with local logging capability

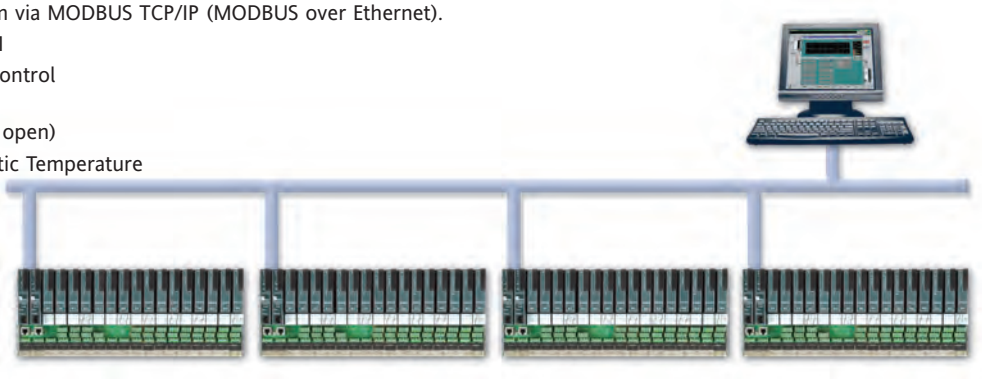
Networking the 6000 series recorders to a central PC for long-term storage of electronic records and remote monitoring of the individual recorder.

The main feature of this offering is security of data in the event of a network breakdown.

- Meets requirements of 21 CFR part 11
- Multiple data recorders
- Local storage
- Optional local display
- Maths capability including Mean Kinetic Temperature
- Not dependant on network
- Bridge and Report software via MS Excel Add-in option
- Time synchronisation

Multiple room monitoring with central logging

This offering includes the EurothermSuite SCADA package combined with T2500 distributed I/O. T2550 I/O units distributed around the plant communicate with the supervisory system via MODBUS TCP/IP (MODBUS over Ethernet).



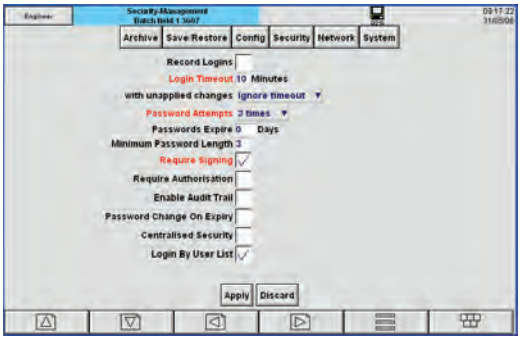
- Meets requirements of 21 CFR part 11
- Accurate continuous and sequential control
- Extensive Maths and Logic libraries (e.g. delay alarms if the room door is open)
- Maths capability including Mean Kinetic Temperature
- Report generation via MS Excel Add-in option
- Cost effective multiple room solution
- Sophisticated alarm functionality
- Time Synchronisation

Fulfilling the Requirements of 21 CFR Part 11

Eurotherm data recorders and process control systems have Electronic Signature and Electronic Record capability. The controllers have a lockout feature that permits changes through a 21 CFR part 11 compliant operator station, thus providing the necessary audit trail.

Tamperproof electronic records

- Process Values and Audit Trails (Alarms, Events, Electronic Signatures)
- Date and Time stamping
- Time Synchronisation
- Viewable in human readable format
- Export conversion facility to MS Excel



Electronic signature

- User actions with Signing and Authorisation
- Unique signatures
- Automatic log-off
- Minimum length password
- Access control according to authority level
- Automatic password expiry
- Traceable audit trail (e.g. in case an attempt is made to gain unauthorised access)

6000 Series data acquisition and management

- Meet requirements of 21 CFR part 11
- Multi-batch recording
- Network-ready via a range of Ethernet protocols
- Maths capability including Mean Kinetic Temperature Calculation
- High precision displays for accurate operator reading
- Remote viewing via Bridge software
- Time synchronisation
- Offline data viewing via Review software
- Report generation via MS Excel Add-in option

EurothermSuite® operation server and viewer

- Meet requirements of 21 CFR part 11
- Client/server architecture with master/backup servers
- Defined display structure
- Trending
- Sophisticated alarm functionality
- Single global database
- Accurate continuous and sequential control
- Extensive Maths and Logic libraries
  (e.g. delay alarms if the room door is open)
- Maths capability including Mean Kinetic Temperature
- Report generation via MS Excel Add-in option
- Time Synchronisation

T2550 Process interface

- Distributed scalable I/O system
- Live plug-in modules
- Direct wiring on a DIN rail mounting
- High accuracy modules
- Standard communications protocols
- Individual module and channel status indication

- **Alarming**
- **Totalisation**
- **Averaging**
- **Reporting**
- **Backup functionality**

Environmental Monitring System

Application Note

Compliance to environmental regulation is now required for any industrial activity. There are very few activities that have zero environmental impact at all. Most work produces waste, burns fuel, uses electricity or carries some risk of pollution.

The Eurotherm Environmental Monitoring System aims at helping to achieve a rigorous approach to managing and improving the environmental aspect of operations required by the ISO 14001 international standard for environmental management systems.

In order to achieve this, the Eurotherm EMS application module provides you with the information and functionality needed to capture the system behaviour and make environmental investment effective.

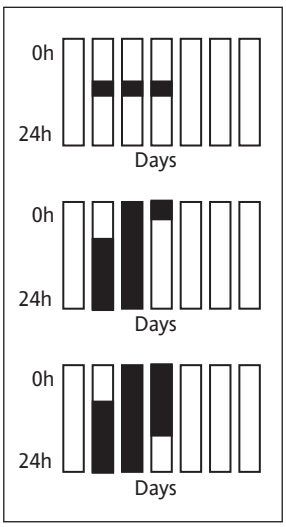
EMS application module functions

- Normal, maintenance and calibration operation modes
- Analogue or digital input type
- Retention of last good value and calculation of a confidence factor if an input fails
- Variable sampling time
- Maximum and minimum PV history
- Totalisation
- Running average calculation
- External reset request of historical data
- Alarm functionality and re-alarming after a preset time

EMS front-end applications

- Selection of tags to average
- Selection of date/time limits focusing on specific time intervals in each day or including all the samples between the date boundaries (see picture)
- Up to three averages calculated at the same time on different time intervals (ranging from minutes to months) on the same group of tags (see Example 1)
- Up to three groups of tags averaged at the same time, each one associated with a different average time interval (see Example 2). This functionality is used to compare actual averages against the maximum authorised average associated to specific monitoring points
- Textual description of the current settings before the calculation begins in order for the operator to check if the report will meet his expectations
- Ability to pause the calculations, view partial reports and restart at a later time or stop the routine
- Ability to print sub-reports including averages from a narrower time interval
- Ability to merge backup files in order to calculate averages over the backup time

Ease of customisation to meet specific requirements

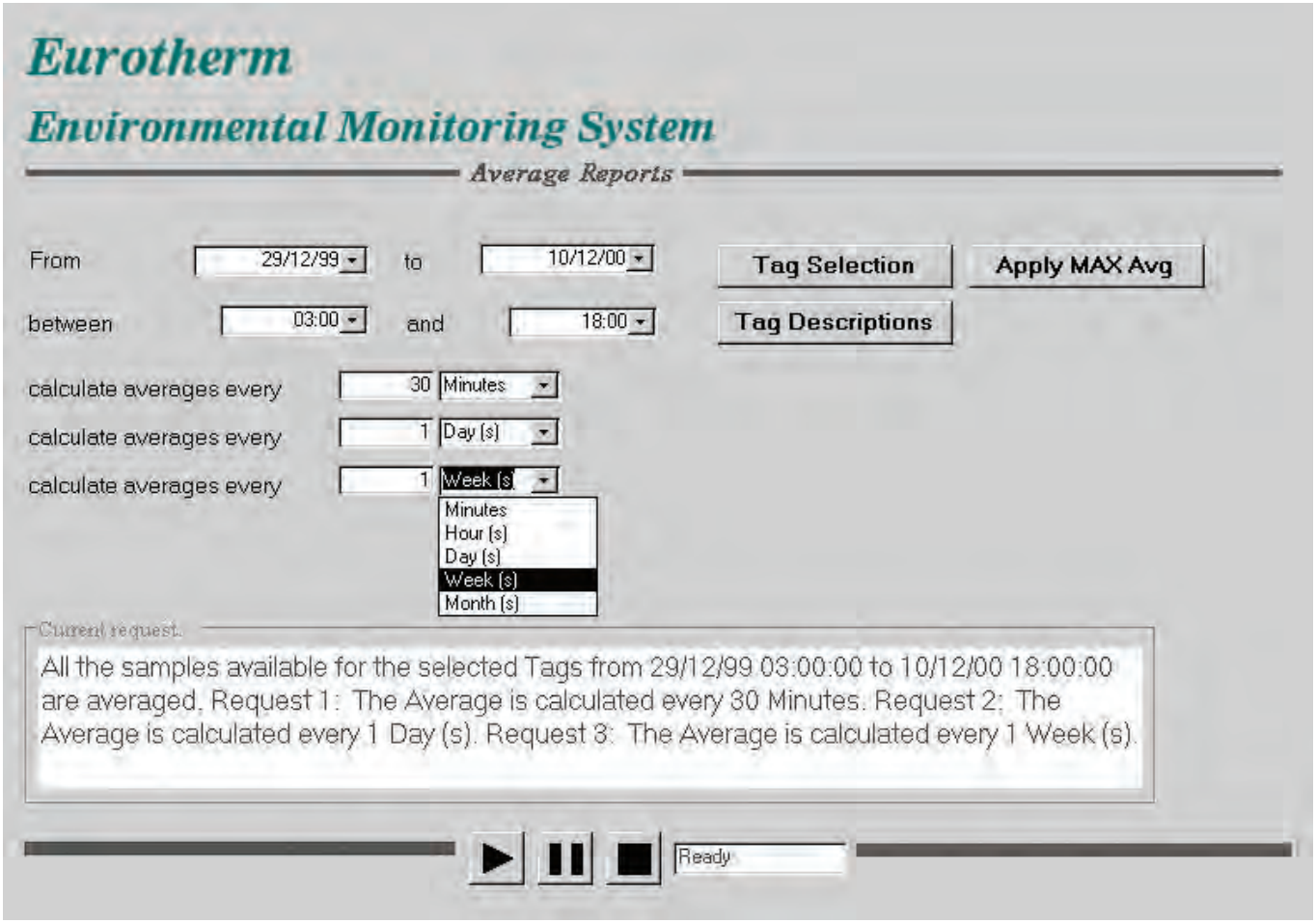


Example 1

On all selected monitoring points calculate:
Avg 1: every 30 mins
Avg 2: every day
Avg 3: every week

Example 2

On monitoring point 1, calculate average every 2 hours
On monitoring point 2, calculate average every 3 days
On monitoring point 3, calculate average every 15 days



- **Non-linearity of the titration curve**
- **Process deadtime**
- **Gain scheduling**
- **Smith predictor**

pH Control
Application Note

Process systems using water such as boilers, CHP plants and water treatment plants, or systems using any types of solution such as those in fermenters, must be designed to take into account the control of pH.

The pH is defined as -log10(aH+); aH+ being the hydrogen ion activity relative to the hydrogen ion concentration;
i.e. $a_{H+} = f_{H+} [H^*]$, where f_{H+} is the activity coefficient of the hydrogen ions, which for diluted solutions is approximately equal to 1, and [H*] is the hydrogen ion concentration.

Robust pH control depends mostly on the following:

- Measurement probe location: For maximum speed of response
- Reaction tank size: Retention time should be minimised
- Reaction tank number: For strong acid-alkali neutralisations, two or three tanks are recommended
- Baffling: Used to avoid whirlpool effects and to prevent the reagents from reaching the pH probe before they have been thoroughly mixed by the agitator
- Mixing and agitation for complete elimination of the areas of unreacted reagent
- Reagent addition point location(s) for close pH control
- Reagent delivery system: Metering pumps for better accuracy or control valves for minimum delivery delay

Two main difficulties are encountered in controlling pH levels.

Non-linearity of the titration curve

The difficulty of pH control stems from the exceptionally wide range of measurement, which covers 14 orders of magnitude of hydrogen ion concentration. It is commonly relied upon to detect changes as small as 10^{-7} moles/litre in hydrogen ion concentration. This incredible range and sensitivity is the result of the non-linear logarithmic relationship of pH to hydrogen ion activity (hydrogen ion concentration in dilute solutions)

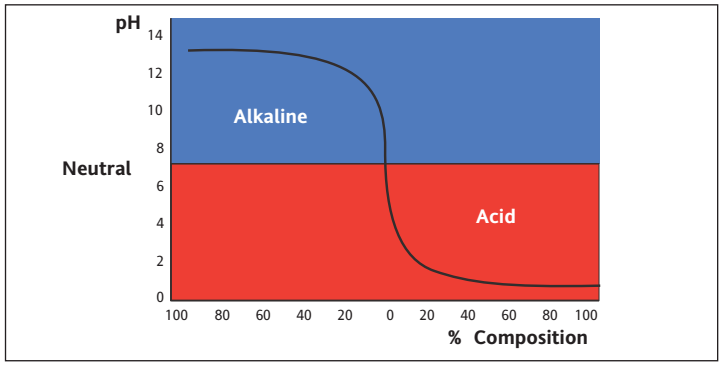


Figure 1 Neutralised curve

The concentrations of the acids and alkalis in solutions determine the pH and shape of the titration (neutralisation) curve shown in Figure 1. This curve shows that the pH is far more sensitive to a change in composition around neutrality than elsewhere.

Process deadtime

The reagents in a tank must be fully mixed and the reaction complete before the pH can be measured accurately and a steady signal received at the controller. The long deadtime in the control loop is a combination of deadtimes from valve deadband, reagent dissolution time, mixing equipment turnover time, mixing equipment transportation delay, electrode lag and transmitter damping.

Gain scheduling

The Eurotherm Process Automation PID control module is designed to address these difficulties.

The non-linearity of the titration curve requires a series of proportional bands which operate in the control loop at different pH levels. The control module can be programmed with as many values for the proportional band and derivative as are required. Switching between proportional band values for each pH band does not result in an output bump.

Deadtime may be reduced by correctly laying out the tank, as in Figure 2, and by fine tuning the PID controller depending on values of the deadtime and process time constant. Influent flow is fed forward to initiate corrective action as soon as changes occur in the process load.

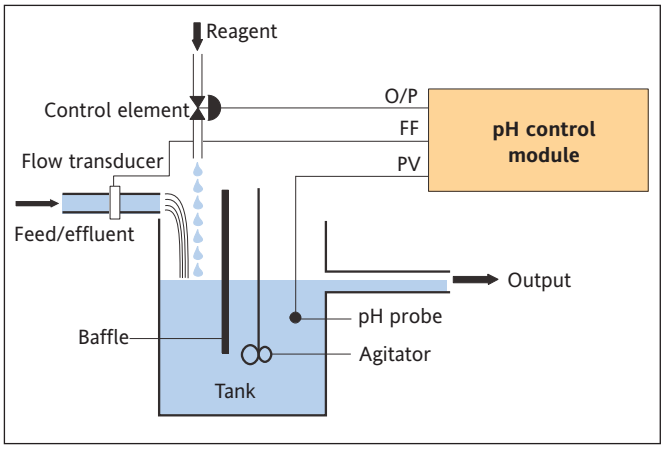


Figure 2 Correct tank layout

Smith predictor

In order to optimise the response time and improve the accuracy of the control strategy, the Eurotherm Process Automation PID control module can optionally include a Smith Predictor algorithm based on a mathematical model of the process.

When the process flow rate is the major load variable, the pH control is improved by configuring the control module as a ratio controller. The objective is to meet increased flow with a corresponding increase in reagent. For this, one loop is dedicated to pH control and uses a Smith Predictor to compensate for the deadtime. The product of the output of the pH loop and the influent flow provides the setpoint to the dedicated reagent flow control loop.

- **Burner modulation**
- **Air/fuel cross-limiting**
- **Regulation of excess air**
- **Oxygen trim**
- **Total heat control**

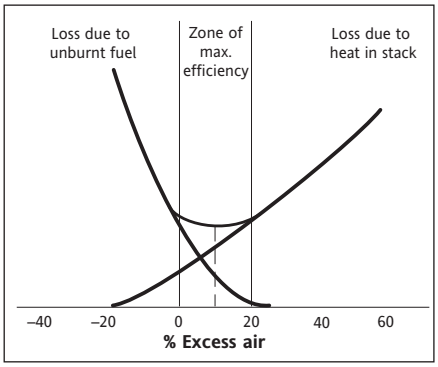
Burner Combustion Control for Boilers

Application Note

Boilers are often the principal steam or hot water generator system used in industrial plant or commercial heating. Consequently, they must be designed to operate efficiently and safely whilst responding rapidly to any change in demand. Burner management systems must be equally adaptive. Eurotherm Process Automation provides efficient, well implemented control techniques capable of reducing operating costs whilst providing resources for greater flexibility in plant management and control. Burner combustion control generally includes one or a combination of the following methods

- Regulation of excess air
- Oxygen trim
- Burner modulation
- Air/fuel cross-limiting
- Total heat control

Excess air regulation



In actual practice, gas, oil, coal burning and other systems do not do a perfect job of mixing the fuel and air even under the best achievable conditions. Additionally, complete mixing may be a lengthy process. Figure 1 shows that in order to ensure complete combustion and reduce heat loss, excess air has to be kept within a suitable range.

Figure 1 Boiler efficiency

The regulation of excess air provides

- A better boiler heat transfer rate
- An 'advance warning' of flue gas problems (excess air coming out of the zone of maximum efficiency)
- Substantial savings on fuel

Oxygen trim

When a measurement of oxygen in the flue gas is available, the combustion control mechanism can be vastly improved (since the percentage of oxygen in flue is closely related to the amount of excess air) by adding an oxygen trim control module, allowing

- Tighter control of excess air to oxygen setpoint for better efficiency
- Faster return to setpoint following disturbances
- Tighter control over flue emissions
- Compliance with emissions standards
- Easy incorporation of carbon monoxide or opacity override

Burner modulation

Modulating control is a basic improvement in controlling combustion. A continuous control signal is generated by a controller monitoring the steam or hot water line. Reductions in steam pressure or hot water temperature lead to an increase in firing rate. The advantages of introducing burner modulation in combustion control include

- Fuel and air requirements are continuously matched to the combustion demand
- Steam pressure or hot water temperature is maintained within closer tolerances
- Greater boiler efficiency
- Weighted average flue gas temperature is lower

Air/fuel cross-limiting

A cross-limiting combustion control strategy ensures that there can never be a dangerous ratio of air and fuel within a combustion process. This is implemented by always raising the air flow before allowing the fuel flow to increase, as shown in Figure 2, or by lowering the fuel flow before allowing the air flow to drop.

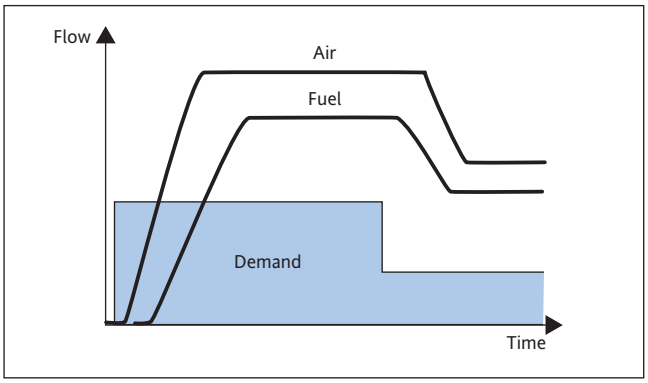


Figure 2 Cross-limiting combustion mechanism

Figure 3 depicts a simplified control block diagram of the cross-limiting combustion circuit. Combination firing of multiple fuels simultaneously can also be easily accommodated within the scheme.

Cross-limiting combustion control is highly effective and can easily provide the following

- Optimisation of fuel consumption
- Safer operating conditions by reducing risk of explosion
- Fast adaptation to variations in fuel and air supplies
- Satisfaction of the plant demand for steam

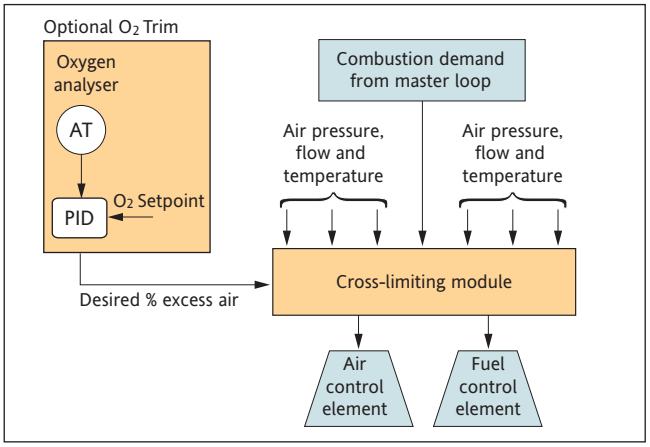


Figure 3 Cross-limiting combustion control with 02 trim

Enhanced cross-limiting

Double cross-limiting combustion control is an enhancement to the above. It is achieved by applying additional dynamic limits to air and fuel setpoints. This translates to having the actual air/fuel ratio maintained within a preset band during and after transition. This method protects against having the demand signal driving the air/fuel ratio too lean, therefore reducing heat loss.

Total heat control

In situations where combustion is not the principal heat source and when several factors contribute to the total heat to be generated by a boiler, a control loop can be introduced in order to monitor and manage the generated heat. This is particularly true for CHP plants, where gas turbines and supplementary firing are used. This type of implementation is shown in Figure 4.

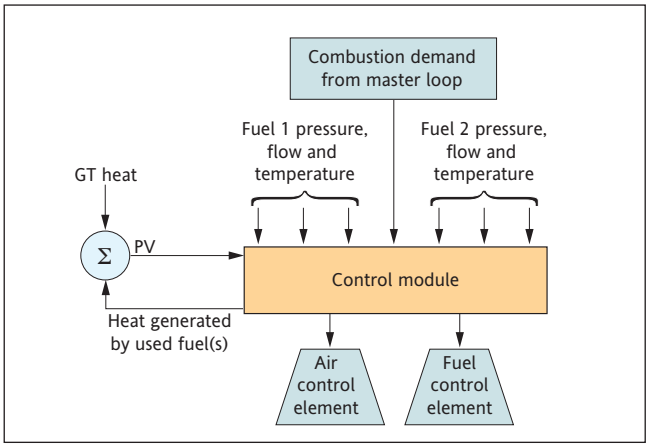


Figure 4 Total heat control

- **Lead/lag selection**
- **Load cycling based on hours run**
- **Load cycling based on time of day**

Pump Sequence Control
Application Note

One of the areas within a boiler plant that is critical to the process is the delivery of boiler feedwater. Depending on the design and functionality, individual feed pumps servicing individual boilers or a bank of feed pumps may maintain a common feedwater pressure that feeds into the boilers.

Implementing pump sequence control allows the system to sequence and cycle pumps such that a minimum number of pumps are needed to maintain the feedwater flow to the boilers requiring it. The pump sequence control can also regulate (where variable speed pumps have been implemented) the output of each pump making its usage more energy efficient.

Pump efficiency is the ratio of the useful output power of the pump to its input power. The typical range of pump efficiencies is from 60 to 85% and is a function of changes in speed, impeller diameter and specific gravity as defined in the following equation

$E_p \mu Sw\ Q\ P_t / P_i$

Where

E_p is the pump efficiency (%)
Sw is the specific weight of the transported liquid (kN/m3)
Q is the pump capacity (m3/s)
P_t is the head pressure (bar)
P_i is the power input (kW)

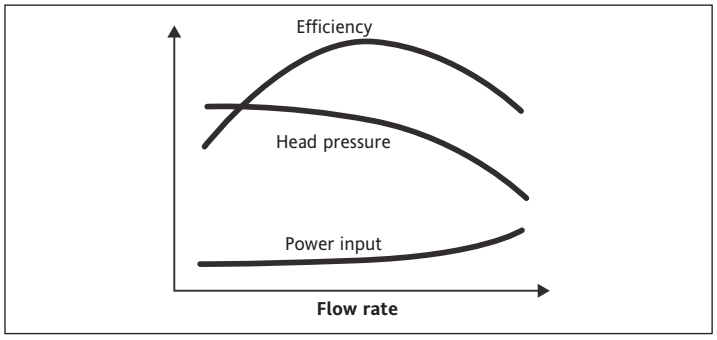


Figure 1 Pump characteristics

At a given impeller diameter and specific gravity, pump flow is linearly proportional to pump speed, pump discharge head relates to the square of pump speed and pump power consumption is proportional to the cube of pump speed. This is why variable-speed pumps can be so highly energy efficient.

A pumping system is optimised when it meets the process demand for liquid transportation at minimum pumping cost in a safe and stable manner.

Once the equipment is installed, the potential for optimisation is limited by the capabilities of the selected equipment, piping configuration and control implementation.

Full automation of pumping stations, including automatic start-up and shutdown and optimised supply-demand matching, offers the following

- Reduction in operating costs
- Protection from loss of control
- Reduced maintenance and cycling
- Increased operating safety as human errors are eliminated

Depending on plant requirements and the type of application, the pump arrangement can be either parallel or serial as shown in Figures 2 and 3.

Series pumping is most effective when the system head pressure curve is steep. When head pressure is not a constraint, parallel pumping is preferred.

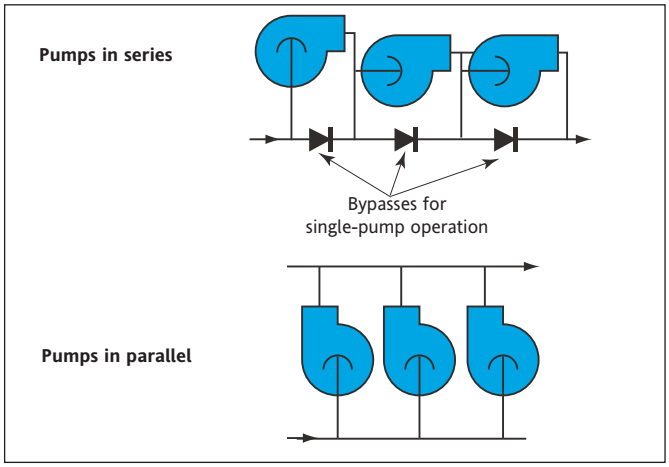


Figure 2 Multiple pump layout

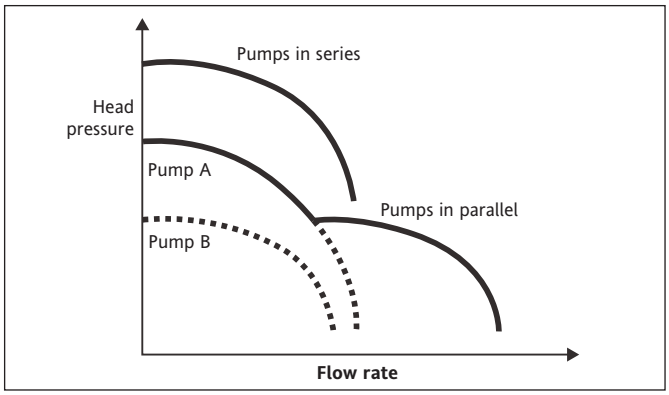


Figure 3 Head pressure - flow rate curves

The Eurotherm control module for pump sequencing allows efficient management of pump load and offers a robust control combined with a powerful man-machine interface.

Lead/lag selection

The control module scheduler arrangement allows the pumps to be run such that the use of each pump is prioritised according to a defined order. If a running pump fails, the next available pump is automatically requested to run.

The pump that is always chosen to run is referred to as the 'Lead' pump. The other pumps are 'Lag' pumps but are prioritised such that a pump with a higher priority always runs before a pump with a lower priority. The lead/lag selection and prioritisation can be set either by the operator or automatically by the application database.

These features mean that

- On an increase of demand, the most efficient pump is started first
- On a decrease of demand, the least efficient pump is stopped first

Features

Management and maintenance activities require a strong and effective man-machine interface, providing the operators, supervisors or plant engineers at any time with an informative and real-time representation of the process.

The control module offers, depending on the application needs, features such as load cycling based on hours run or time of day. Flexibility and ease of configuration combined with a powerful functionality make this control module an essential element in industry applications requiring high efficiency pumping systems at reduced operating costs.

- **Two and three element drum level control**
- **Enhanced three element drum level control**

Boiler Drum Level Control
Application Note

The purpose of the drum level controller is to bring the drum up to level at boiler start-up and maintain the level at constant steam load. A dramatic decrease in this level may uncover boiler tubes, allowing them to become overheated and damaged. An increase in this level may interfere with the process of separating moisture from steam within the drum, thus reducing boiler efficiency and carrying moisture into the process or turbine.

The functions of this control module can be broken down into the following:

- Operator adjustment of the setpoint for drum level
- Compensation for the *shrink & swell* effects
- Automatic control of drum level
- Manual control of the feedwater valve
- Bumpless transfer between auto and manual modes
- Indication of drum level and steam flow
- Indication of feedwater valve position and feedwater flow
- Absolute/deviation alarms for drum level

The three main options available for drum level control are:

Single-element drum level control

The simplest but least effective form of drum level control.

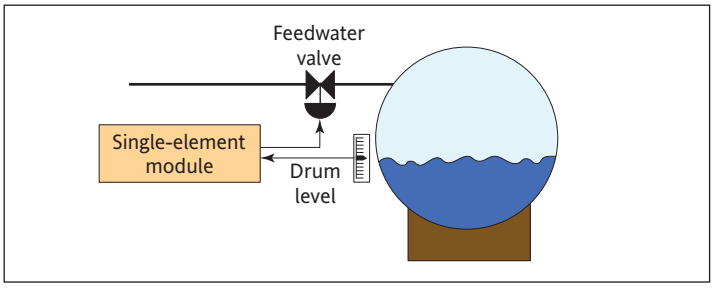


Figure 1 Single-element drum level control

This consists of a proportional signal or process variable (PV) coming from the drum level transmitter. This signal is compared to a setpoint and the difference is a deviation value.

This signal is acted upon by the controller which generates corrective action in the form of a proportional output. The output is then passed to the boiler feedwater valve, which then adjusts the level of feedwater flow into the boiler drum.

Notes:

- Only one analogue input and one analogue output required
- Can only be applied to single boiler / single feedpump configurations with relatively stable loads since there is no relationship between drum level and steam- or feedwater flow
- Possible inadequate control option because of the *swell* effect

Two-element drum level control

The two-element drum level controller can best be applied to a single drum boiler where the feedwater is at a constant pressure.

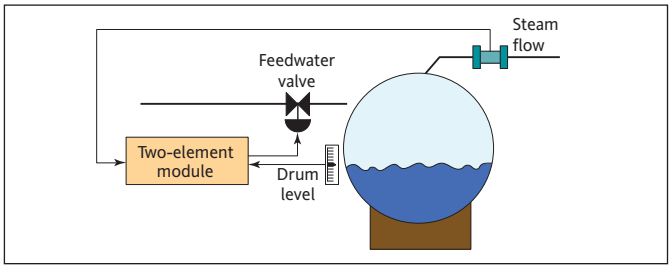


Figure 2 Two-element drum level control

The two elements are made up of the following:

Level Element: a proportional signal or process variable (PV) coming from the drum level transmitter. This signal is compared to a setpoint and the resultant is a deviation value. This signal is acted upon by the controller which generates corrective action in the form of a proportional value.

Steam Flow Element: a mass flow rate signal (corrected for density) is used to control the feedwater flow, giving immediate corrections to feedwater demand in response to load changes.

Any imbalance between steam mass flow out and feedwater mass flow into the drum is corrected by the level controller. This imbalance can arise from:

- Blowdown variations due to changes in dissolved solids
- Variations in feedwater supply pressure
- Leaks in the steam circuits

Notes:

- Tighter control of drum level than with only one element
- Steam flow acts as feed forward signal to allow faster level adjustments
- Can best be applied to single boiler / single feedpump configurations with a constant feedwater pressure

Three-element drum level control

The three-element drum level control is ideally suited where a boiler plant consists of multiple boilers and multiple feedwater pumps or where the feedwater has variations in pressure or flow.

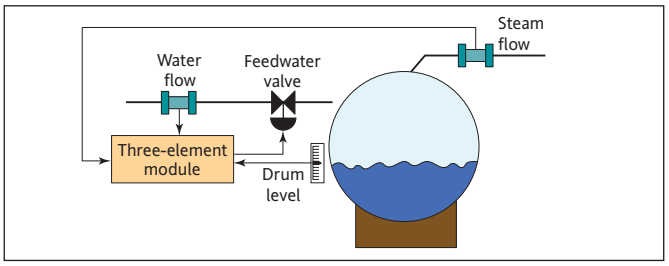


Figure 3 Three-element drum level control

The three-elements are made up of the following:

Level Element and Steam Flow Element: corrects for unmeasured disturbances within the system such as:

- Boiler blowdown
- Boiler and superheater tube leaks

Feedwater Flow Element: responds rapidly to variations in feedwater demand, either from the

- Steam flow rate feedforward signal
- Feedwater pressure or flow fluctuations

In order to achieve optimum control, both steam and feedwater flow values should be corrected for density.

Notes:

- The three-element system provides tighter control for drum level with fluctuating steam load. Ideal where a system suffers from fluctuating feedwater pressure or flow
- More sophisticated level of control required
- Additional input for feedwater flow required

Enhanced three element drum level control

The enhanced three-element drum level control module incorporates the standard three element level components with the following improvements:

- The three-element mode is used during high steam demand. The two-element mode is used if the steam flow measurement fails and the module falls back to single element level control if the feedwater flow measurement should fail or if there is a low steam demand.
- The drum level can be derived from up to three independent transmitters and is density compensated for pressure within the boiler drum.

Notes:

- Tighter control through a choice of control schemes. Drum level maintained on failure of steam or feedwater flow measurements
- This module introduces an additional level control loop Boiler drum level control

- **Two and three element drum level control**
- **Enhanced three element drum level control**

Boiler Blowdown Control
Application Note

Before boiler feedwater is passed into the boiler, it must be chemically treated to remove the corrosive elements that may be present and would ultimately corrode the boiler as well as affect the quality of steam required within a process.

Chemicals entering the boiler via the feedwater must be removed from the boiler. Failure to do so can result in the boiler system suffering from scale formation, corrosion, brittle and cracking metal, carry-over and foaming. Therefore a proper chemical balance must be maintained within the boiler itself.

This is achieved through blowdown control. This process involves activating the blowdown valve mechanism situated on the boiler drum and drawing off a small percentage of the boiler water (containing the dissolved solids and non-dissolved sediments) from below the surface of the water in the boiler.

In order to retain a chemical balance within the boiler, the quantity of chemicals removed from the drum via blowdown must be equal to the quantity of chemicals that enter through feedwater. As steam loads vary, the rate of feedwater changes and so does the rate of blowdown.

On the other hand, excessive blowdown leads to inefficient running of the boiler plant, as each blowdown causes heat contained within the expelled water to be lost. The cost of fuel can be directly related to this heat loss. The cost of water and chemicals should also be taken into account. A balance has to be established between the requirements of removing the dissolved solids from the boiler system and running the boiler plant cost-effectively.

A boiler, operating at 80% efficiency, has a maximum evaporation rate of 5,000kg/hr at 10 bar and receives feedwater at 70°C. Of the 5,000kg/hr, 4,500kg/hr of steam is exported and 500kg/hr is lost through blowdown. Using steam tables, the heat content of the water and steam is calculated to be

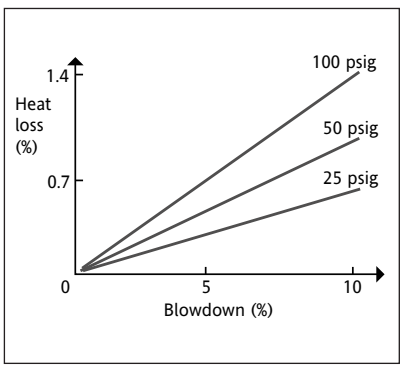
4,500kg/hr (2,357kJ/kg = 9,621,274kJ/h
500kg/hr (357 kJ/kg = 178,500 kJ/h

giving a total of

9,799,774kJ/h or 2,723kW

The above example is typical of a modern boiler plant using base exchange softening only. Blowdown rates are much lower when de-mineralised feedwater is used. In the example, the heat loss is equivalent to 1.8% of the fuel fired.

Operated continuously over a year the fuel wasted per boiler represents approximately 46,500 m^3 of natural gas, 44,500 litres of fuel oil or 70 tonnes of coal. Added to this is also the cost of acquiring and treating the water that is used within the boiler system.



Blowdown control can be broken down into instantaneous or continuous systems and may be manual, semi-automatic or fully automatic.

Instantaneous manual system

The simplest implementation of blowdown control is an instantaneous manual system that is operated once per shift to reduce the boiler total dissolved solids (TDS) to a sufficient level well below the boiler specified maximum limit. The TDS are then allowed to build up during the next shift until they reach the maximum level again.

A TDS test should be carried out prior to blowdown so that the time can be adjusted to reflect changes in average boiler load conditions which may occur on a day-to-day basis.

Advantage:

- Easily implemented with relatively low sensor outlay

Disadvantage:

- Load fluctuations are not taken into account. Heat recovery from blowdown is expensive and difficult

Automatically timed control

Figure 2 shows a simple semi-automatic system where a timer is used to control blowdown for short periods according to a pre-set schedule. Again, with this system, daily testing of the boiler is necessary so that the timing schedule can be adjusted to take into account changes in boiler and system operation.

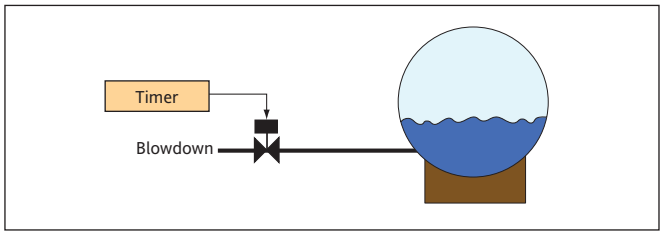


Figure 2 Automatically timed blowdown control

The system can be made fully automatic by installing a TDS monitoring facility as pictured in Figure 3. This will override the timer in the event of variation from the desired TDS level.

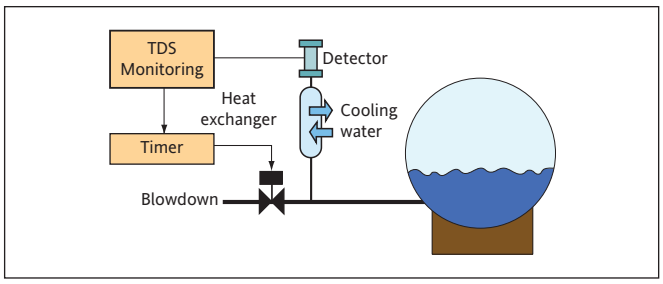


Figure 3 Automatic blowdown control with TDS monitoring

Disadvantage:

- Standard fully open/closed valve provides coarse control

Continuous control

Continuous blowdown systems are preferable where heat recovery is required. In its simplest form, such a system consists of a valve, adjusted after regular boiler water testing. The valve position is determined from the boiler pressure, TDS levels and the blowdown rate required.

As shown in Figure 4, a control module is used to modulate the blowdown valve using inputs from a TDS detector located in the cooled blowdown sidestream. For this system to operate correctly, cooled blowdown must flow continuously over the detector.

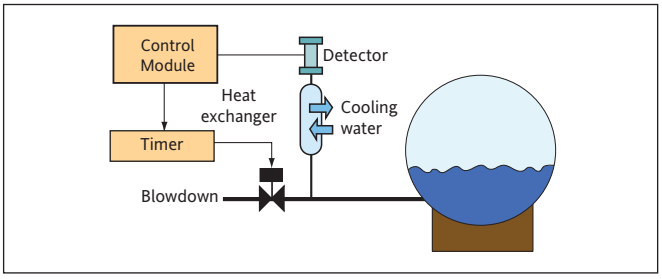


Figure 4 Continuous blowdown control

Advantage:

- Smaller and cheaper heat recovery plant
- Possibility of recovering up to 50% of the heat in the blowdown

Intermittent blowdown

Blowdown can also be achieved in the boiler evaporators where sediments are deposited. This process is carried out intermittently by opening the appropriate valve and allowing the sediments to be flushed out.

Combined control

Eurotherm offers a control module that can be configured for continuous, intermittent or both continuous and intermittent blowdown control.

- **Operator selection of Duty/Standby device**
- **Changeover on device failure or process condition**
- **Bumpless transfer**
- **Equipment status and hours run indication**

Duty/Standby Control Module
Application Note

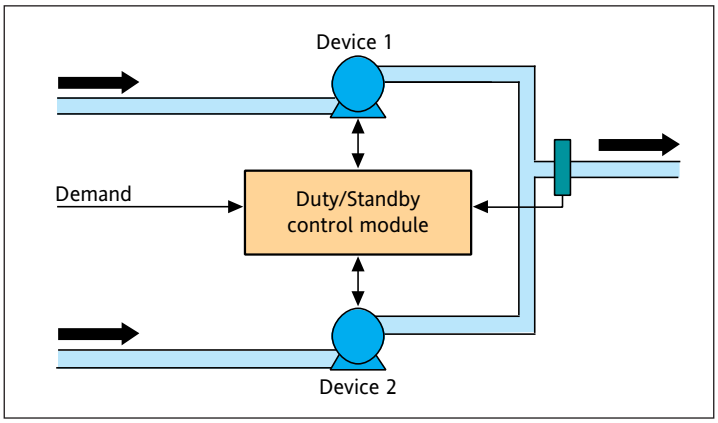
Plant activities that may be deemed critical require a higher level of backup functionality. This can be in the form of a pump or other device set. In order to deliver this backup functionality, these device sets must be able to automatically react to plant conditions such as device failure.

In addition to the plant backup facilities, device sets can also allow for equal workload distribution and offer 'maintenance-aware' options such as hours run logging and automatic changeover.

One of a range of control modules designed by Eurotherm Process Automation, incorporating efficient control techniques and supplying this functionality, is the Duty/Standby control module.

The Duty/Standby arrangement allows a pair of devices - typically On/Off or variable speed drives - to be operated with an element of redundancy. Each device is capable of matching the plant demand and, thus, normally only one device is run at any one time. Should the running device fail, the remaining device is automatically requested to run.

One device is referred to as the 'Duty' while the other device is the 'Standby'. The choice of which device acts as Duty is known as the Service. In normal running operation, the Duty is running and the Standby is stopped.



Some of the functions provided by the Duty/Standby control module are:

- Operator selection of Duty/Standby device when in Manual
- Changeover on device failure or process condition when in Automatic
- Bumpless transfer
- Equipment status and hours run indication

Operator selection of Duty/Standby device

In normal running operations, the operator may request a changeover such that the Standby device is started. When the control module successfully starts the Standby device, the Service is changed. Following a Duty device failure, the operator may also request to 'make duty' the running Standby without altering the state of either device.

Changeover on device failure or process condition

The control module may act, as a result of a single failure or a process condition, by scheduling the control devices in a single direction only, i.e. automatically starting the Standby device as a result of the failure of a running Duty device but not starting the Duty device if the Standby device fails.

Bumpless transfer

Mode selection (Manual or Auto) is initiated by the operator with bumpless transfer, preventing abrupt changes in the output that could otherwise cause damage to field equipment and destabilise the plant process.

Equipment status and hours run indication

The control module offers a comprehensive Man-Machine Interface by providing continuous monitoring of device status and alarming capabilities. It can also offer additional features such as running time for each device for maintenance purposes.

Some of the advantages offered by the implementation of a Duty/Standby device set are

- Redundancy
- Easier maintenance
- Quick diagnosis of failures
- Reduction/elimination of down time

Demand Load Management
Application Note

One of the primary goals in operating a boiler plant is to ensure that the working steam pressure (or temperature in hot water systems) is sustainable for any load demand placed on the plant. At the same time, this requirement must be met as efficiently and cost effectively as possible.

In a multi-boiler plant, this can be achieved through the implementation of demand load management, the purpose of which is to distribute the steam demand in an optimised manner and to adjust the boiler plant output to meet working requirements. This ensures that boilers are fired only when required, thus reducing running costs. Alternatively, demand load management can allow each boiler to be allocated the same amount of running time.

The Eurotherm application module for demand load management offers a comprehensive set of functions, some of which are described below.

- **Operator selection of baseload or modulating operation**
- **Parallel or serial demand sharing**
- **Boiler banking**
- **8-day timer**
- **Multi-sequence programme selection**

Operator load allocation

The demand share arrangement allows each boiler to be operated in either base-load or modulating service, finding the best distribution of load between the boilers that will result in the lowest overall cost.

The base-load operation leaves the implementation up to the operator. In this mode, the total demand is shared between the baseload boilers in proportion to the operator set base-load values. The modulating mode of operation, on the other hand, enforces automatically the load allocation without the need for operator intervention. The total demand, less that satisfied by the base-load boilers, is shared between the modulating boilers in proportion to their capacities. The flexibility of the control module is such that one combination of boiler modes can be applied dynamically to the boiler plant.

Demand sharing

In boiler plants, the most effective load allocation is not based on a simple operating decision but on real-time calculations taking into account the following

- Operating safety margins
- Load fluctuations
- Required shut-down characteristics
- Boiler capacities

A further important decision involves the demand sharing methodology, which can be either parallel or series, depending on plant requirements. The Eurotherm control module allows for both configurations.

In parallel, the available boilers share the total demand simultaneously by taking up an equal firing rate to meet the load. On load increase, the firing rate of all modulating boilers will increase equally until the load requires an additional boiler. At this point, the firing rate of the active boilers decreases to compensate for the firing rate of the newly started boiler. Figure 1 explains the process for an increase of load.

Parallel modulation is generally implemented for steam boilers. It offers the most effective control when relatively steady process loads are available. As the system modulates the boiler plant to adjust the common header pressure to the required setpoint, a smoother response to changing load conditions is performed by the controller.

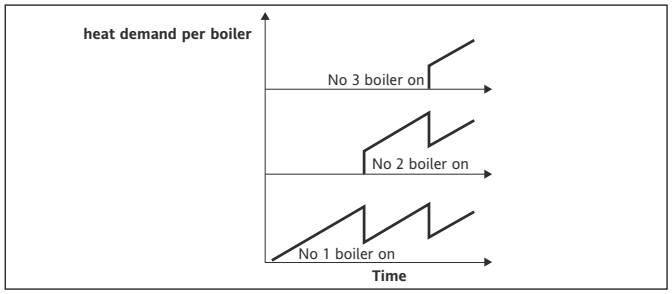


Figure 1 Parallel Demand Sharing

Series demand sharing allocates loads by normally forcing one boiler at a time to modulate in order to satisfy the demand and is most effective when used with the Eurotherm demand schedule control module. On load increase, the firing rate of the modulating boiler will increase until the load requires an additional boiler. At this point, a new boiler is started and becomes the modulating boiler. The other active boilers are ramped to their optimum firing rate. Figure 2 explains the process for an increase of load.

Series modulation is generally implemented for hot water systems or fluctuating steam loads. This mode allows faster individual boiler response to plant conditions as the boiler pressure is adjusted to the required setpoint.

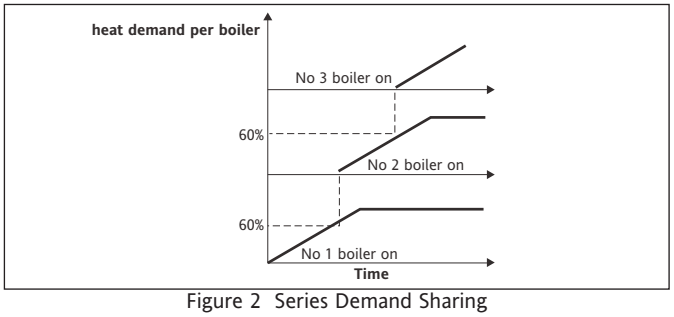


Figure 2 Series Demand Sharing

The boilers that are chosen to always run are referred to as the 'lead' boilers. All the other boilers are 'lag' boilers but are prioritised such that a boiler with a high priority always runs before a boiler with a low priority and so on. E.g. the most effective boiler is always started first and the least effective one is always stopped first.

Boiler banking

This functionality is achieved by keeping the available boilers in hot standby mode until required to fire. This is achieved by ntermittently firing the unused boilers, thus maintaining a required pressure by use of upper and lower banking thresholds or by recirculation of return water through the boilers to keep them hot. The main advantage of boiler banking is that it acts a 'warm' start facility improving the plant response to sudden load changes.

8-day timer

Further enhancement to the man machine interface is achieved by the 8-day timer facility depicted in Table 1. Boiler banking is tabulated according to daily upper and lower banking threshold pressures with an additional user definable 'Today' schedule to be loaded if and when required. Up to four optional session settings can be pre-configured and stored at the supervisory computer.

Logical Boiler	Today	Mon	Tue	Wed	Thurs	Fri	Sat	Sun
Session No.	Hi	Hi	Hi	Hi	Hi	Hi	Hi	Hi
	Lo	Lo	Lo	Lo	Lo	Lo	Lo	Lo

Table 1 Boiler Banking 8-Day Timer

Multi-sequence programme selection

In order to meet the plant demand with savings on fuel consumption, the boiler dispatching can be automated via a multi-sequence programme selection. The boiler duties can then be scheduled according to configurable daily sessions or sequences of events. The effects of this feature are

- Flexibility
- Reduction in operating decisions
- Robust control implementation
- Expandability

Demand load management is an optimising function that augments, but does not replace, the combustion control system.

INDUSTRY

- **Compensation for water loss**
- **Reduction in operating costs**

Make-up Water Control
Application Note

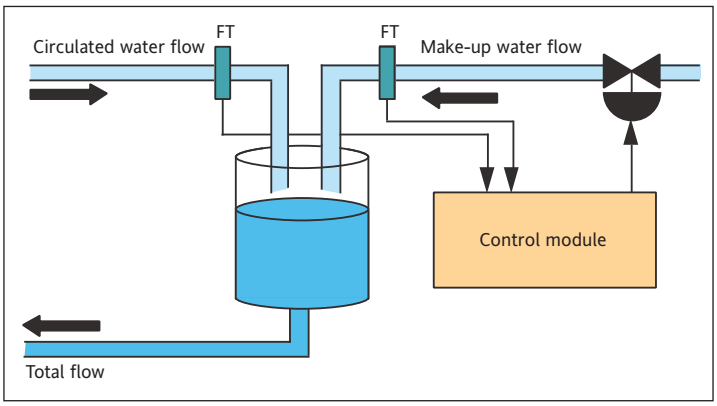
Process systems using water such as boilers and water treatment plants must be designed to operate efficiently whilst responding to any changes in demand. In these processes, water is generally lost in the recirculation by evaporation, drift, blowdown or leakage. Eurotherm® provides an efficient, well implemented control technique capable of reducing operating and pumping costs whilst providing resources for greater flexibility in plant management and control.

The illustrated control loop uses a PID control module to regulate the total water flow in the recirculation system by adding make-up water to the circulated water.

The circulated water flow in the plant is measured, linearised within the control module and compared with the required total flow setpoint. The resultant value is then used as a setpoint for the make-up water flow control loop.

Make-up water control provides

- Plant efficiency
- Faster return to optimal operating levels
- Substantial savings on operating costs



Life Sciences

INDUSTRY

- **Building Management Systems**
- **Environmental Monitoring Systems**

Complete BMS and EMS Solutions from Eurotherm

Application Note

Why BMS/EMS?

"Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented and reviewed." FDA 21 CFR Part 820.70 Production and Process Controls, section c.

Control and monitoring of storage and production environments has become an important issue within the Pharmaceutical Industry. The FDA, EMEA and other regulatory bodies require accurate measurement and storage of room parameters and, if the storage medium is electronic, the methods used must comply with 21 CFR Part 11.

The FDA also states in its 21 CFR part 203.32 that: *"Manufacturers; authorised distributors of record and their representatives shall store and handle all drug samples under conditions that will maintain their stability, integrity and effectiveness and ensure that the drug samples are free of contamination, deterioration, and adulteration."*

Other FDA rules related to environmental control and monitoring include:

- 211.42: Design and construction features (section 10)
- 211.46: Ventilation, air filtration, air heating and cooling
- 211.142: Warehousing procedures (section b)
- 820.70: Production and process controls
- ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (sections 4.2 and 10)

Application Notes

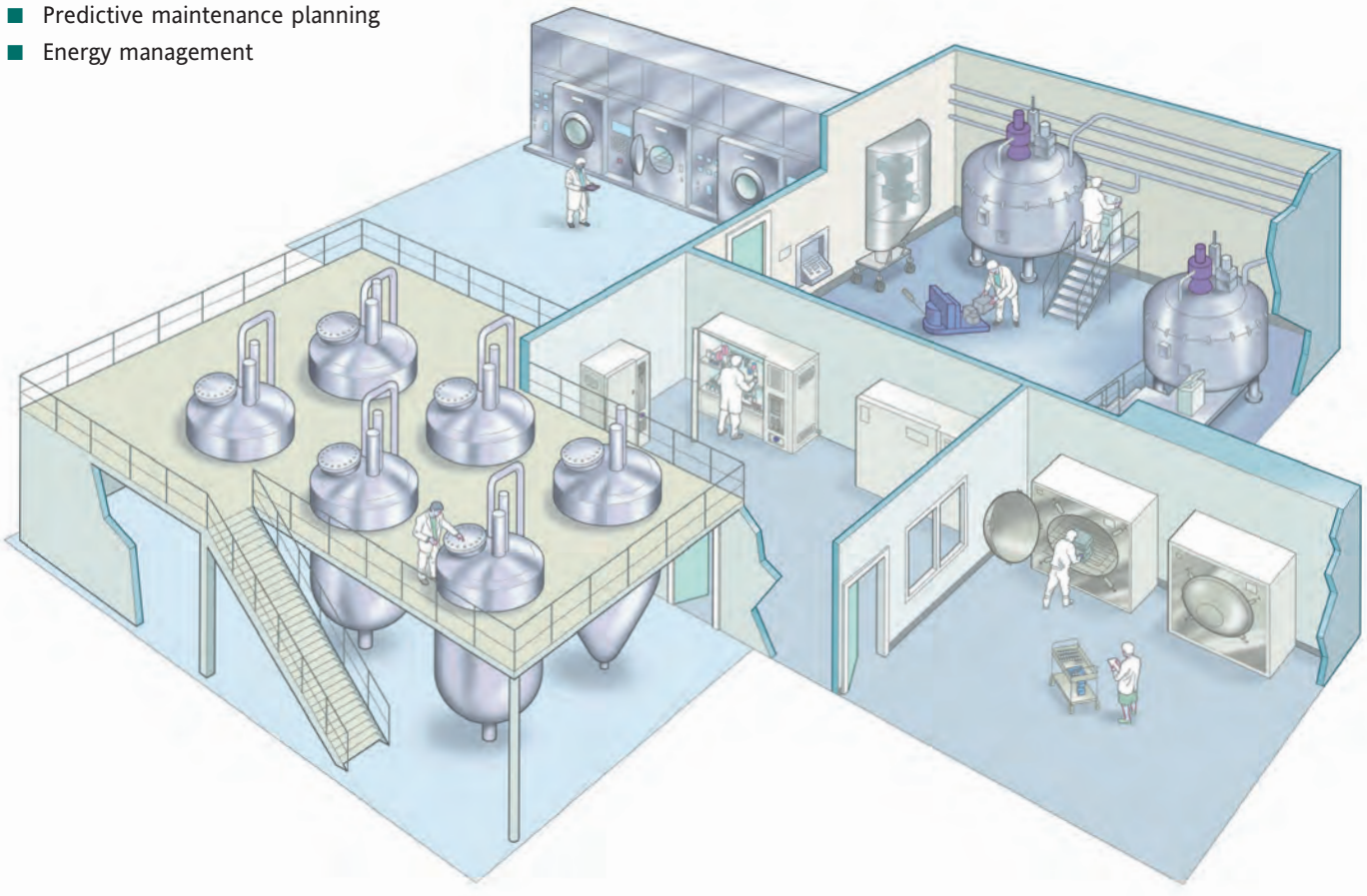
Complete BMS and EMS Solutions from Eurotherm

Complete BMS and EMS Solutions from Eurotherm

Why Eurotherm?

The Eurotherm BMS/EMS system is designed to satisfy the requirements of regulatory bodies including 21 CFR Part 11 and it offers:

- Scalable from a single room to a plant wide solution
- Simplifies validation using flexible and modular standard functions
- Accurate and effective control of HVAC systems and other related equipment
- Centralized and/or remote control of facilities and equipment
- Real time Monitoring of BMS performance
- Intelligent alarm capability for early warning of process deviations
- Corrective strategies when stability factors go outside the specification
- Secure management and storage of environmental data and audit trails
- Predictive maintenance planning
- Energy management

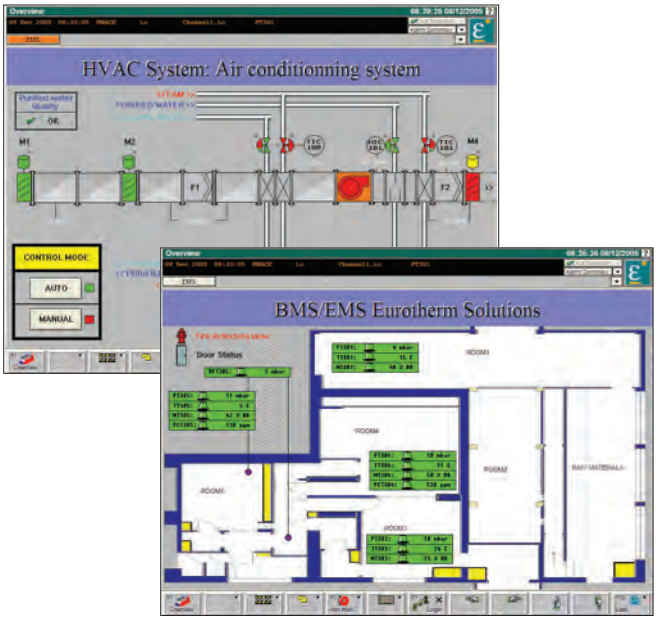


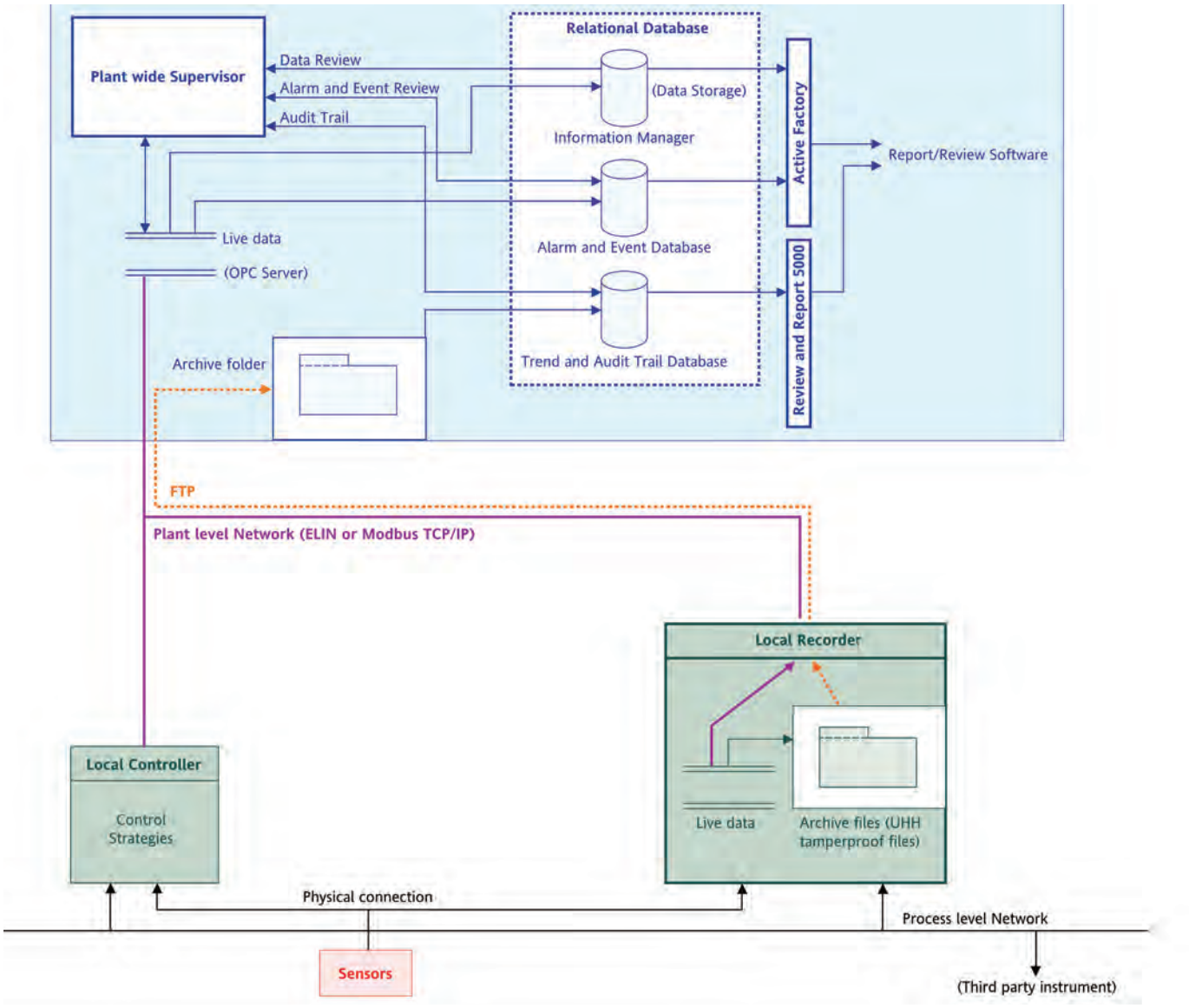
Scalable BMS/EMS Solutions from Eurotherm

Eurotherm Building Management Systems provide Control, Monitoring, Recording and Alarming of a range of facilities within a plant including:

- Production facilities including Aseptic areas
- Laboratory facilities
- Warehouse facilities
- Cold storage facilities
- Environmental Chambers
- Office facilities
- Fire and alarm security systems
- Water purification systems

Not all existing BMS systems offer a logging facility and, for these systems an independent monitoring system, EMS, will be needed. Typically an EMS will provide independent monitoring and logging of the critical environmental parameters for GMP, GLP and GDP facilities.





Flexible and Modular BMS/EMS Solution

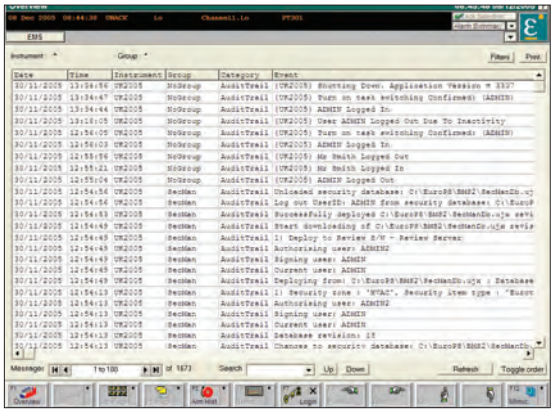
Eurotherm BMS/EMS Standard Modules

Eurotherm BMS/EMS solutions are modular and scalable. They offer all the functionality required to control, monitor, record and alarm, for a single room to a plant wide application. They are ideal for

- Implementing a new system
- Enhancing existing systems
- EMS for an existing BMS

It offers the options for:

- Centralised BMS/EMS
- Network of local standalone BMS/EMS units
- Combination of centralised and local systems to increase availability and ease of use



Sensor

Sensors communicate measurement and status information from the process to the control and monitoring modules of the BMS/EMS system. Sensors include:

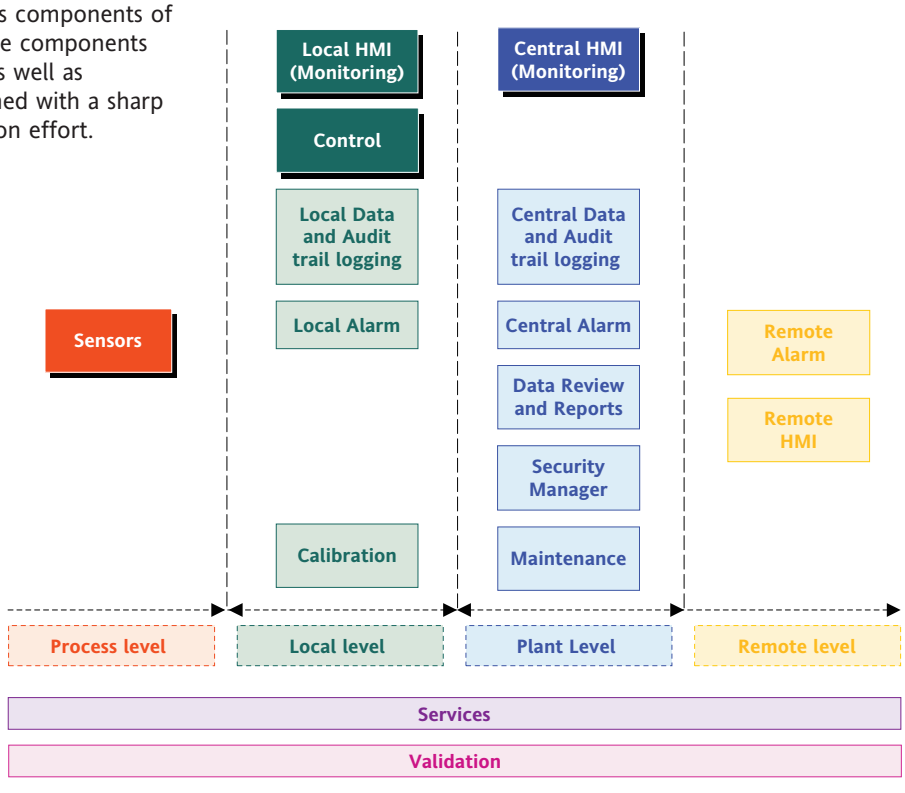
- Temperature
- Relative Humidity
- Air pressure or differential pressures
- Luminescence (light level)
- Particle counters
- Air Flow patterns
- Gas Level
- Vibration
- Noise
- Water leak detection
- Doors status
- Fire detectors
- HVAC healthy status

For hazardous rooms intrinsically safe devices must be used including:

- Intrinsically Safe sensors
- Intrinsically Safe barrier
- Intrinsically Safe IO modules

Eurotherm can offer a range of the above sensors or alternatively provide interface to sensors supplied by the user.

The block diagram demonstrates the various components of the Eurotherm BMS/EMS system. All of these components are standard functions of the system and, as well as providing necessary functionality, are designed with a sharp focus on ease of use and to reduce validation effort.



Accurate Control with Redundancy Option

Monitoring

BMS/EMS offer a wide range of options for monitoring the plant. Information can be monitored locally, centrally and remotely. Access to the system is protected. Users must login to gain access to functionality, defined by their access level.

Plant information is monitored through standard and custom displays and includes:

- Live data
- Mimics with live data
- Multi language support

Information received from the plant is grouped together in various forms to allow the users to rapidly access the required information. The system utilises an easy to use, hierarchical methodology of presenting the necessary information to the users including:

- Plant overview
- Area overview
- Individual room overview
- Individual control loop view
- Individual sensor view
- Grouping by type (e.g. temperature, humidity, pressure)

Data collected from the plant are linked together and displayed as trends using online and historical trending within the system. Trended data are available in various groups e.g. by room, by type (temperature, pressure etc.)

The monitoring facility also provides the user with access to standard features of the system according to their access level, including:

- Access control with password protection for individual user accounts, inactivity timeout and password expiry
- Alarms
- Trends
- Alarm set point configuration
- Control parameter configuration
- Calibration facilities
- Maintenance facilities
- Batch displays
- Electronic signatures
- Configuration utilities
- Multi language support

Control

The purpose of this component is to provide the control of the necessary parameters for each individual room/area.

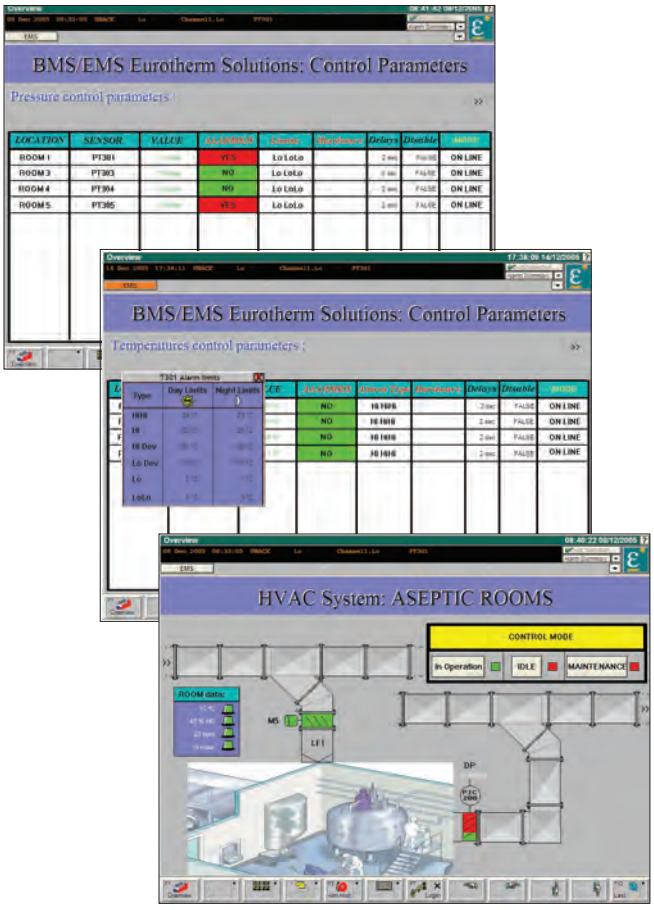
It offers standard control functionality, e.g. PID loops, to accurately control the various environmental conditions of the room.

It also provides the functionality required to control devices such as pumps, motors and valves, e.g. start/stop with necessary interlocks. Operation can be configured to be automatic, semi-automatic, manual or any combination of these.

Individual rooms/areas may be operated in different modes; the selecting of which is access controlled by authorised users:

- Idle: Option for turning off the control of the critical parameters
- In operation: Automatic control of critical parameters
- Maintenance: Automatic and Manual control of critical parameters. This mode is also used for calibration of sensors.

BMS offer the facility for adjusting control parameters (e.g. setpoints, alarm limits, tolerances, time delays) in order to achieve the desired condition in each room. This feature is only available to users with the appropriate access permissions. The system provides a full audit trail of these changes including electronic signatures.



Data Logging and Audit Trail Designed to Satisfy 21 CFR Part 11

Data Logging

Data logging is a key requirement for BMS/EMS systems. 21 CFR Part 11 requires that logged data will be tamper proof and will include critical environmental parameters (temperature, humidity, pressure, particulate sizes, etc), with audit trails including:

- Accurate time and date stamps
- Alarms and events
- User actions and details (e.g. setpoint changes)
- User notes
- Electronic Signatures
- Login/Logout

Eurotherm's BMS/EMS systems log plant data to tamper proof files and SQL relational databases. Data logging can be offered as:

- Local logging (Tamper proof file)
- Central logging (SQL database)
- Local and central logging (Tamper proof files and SQL database)

The availability of logged data can be significantly increased by the local and central logging option. This allows data collection in multiple devices to further protect vital plant data.

Typically a BMS/EMS system comprises of a number of distributed units where each unit has its own internal clock. Time synchronisation is included to ensure accurate time and date stamps, as required by 21 CFR Part 11, to a known clock source.

The BMS/EMS system offers provisions for electronically copying data for archive and export facility to common packages (e.g. Excel, Word, PDF, etc.) for viewing of secure records in human readable format. Other features of the system include:

- Power and network recovery automatic procedures
- FTP server to put the data on a central server
- Scheduled transfers

The system can be configured to provide logging for non-critical parameters including:

- System events
- Equipment failure
- Equipment performance and maintenance
- Energy usage

Alarms and Events Reporting

An important feature of the BMS/EMS system is its Alarms and Events functionality. All alarms and events are time stamped and logged for long term retention and validation to 21 CFR Part 11. Individual plant data can be configured to have one or a combination of the following alarms:

- Absolute alarms
- Deviation alarms
- Rate of Change alarms
- Delayed alarms
- Excursion alarms

The system can be configured to provide other alarms including;

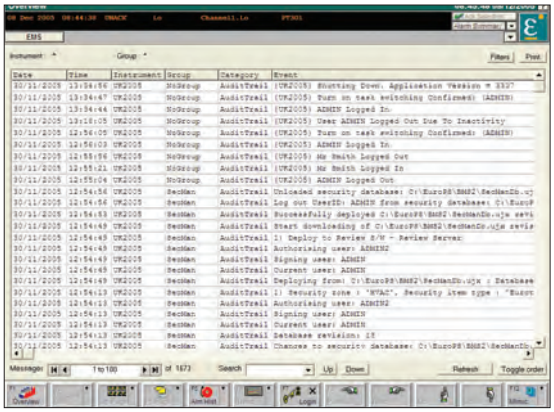
- Sensor break
- Equipment failures
- Network failure
- Maintenance and calibration alarm

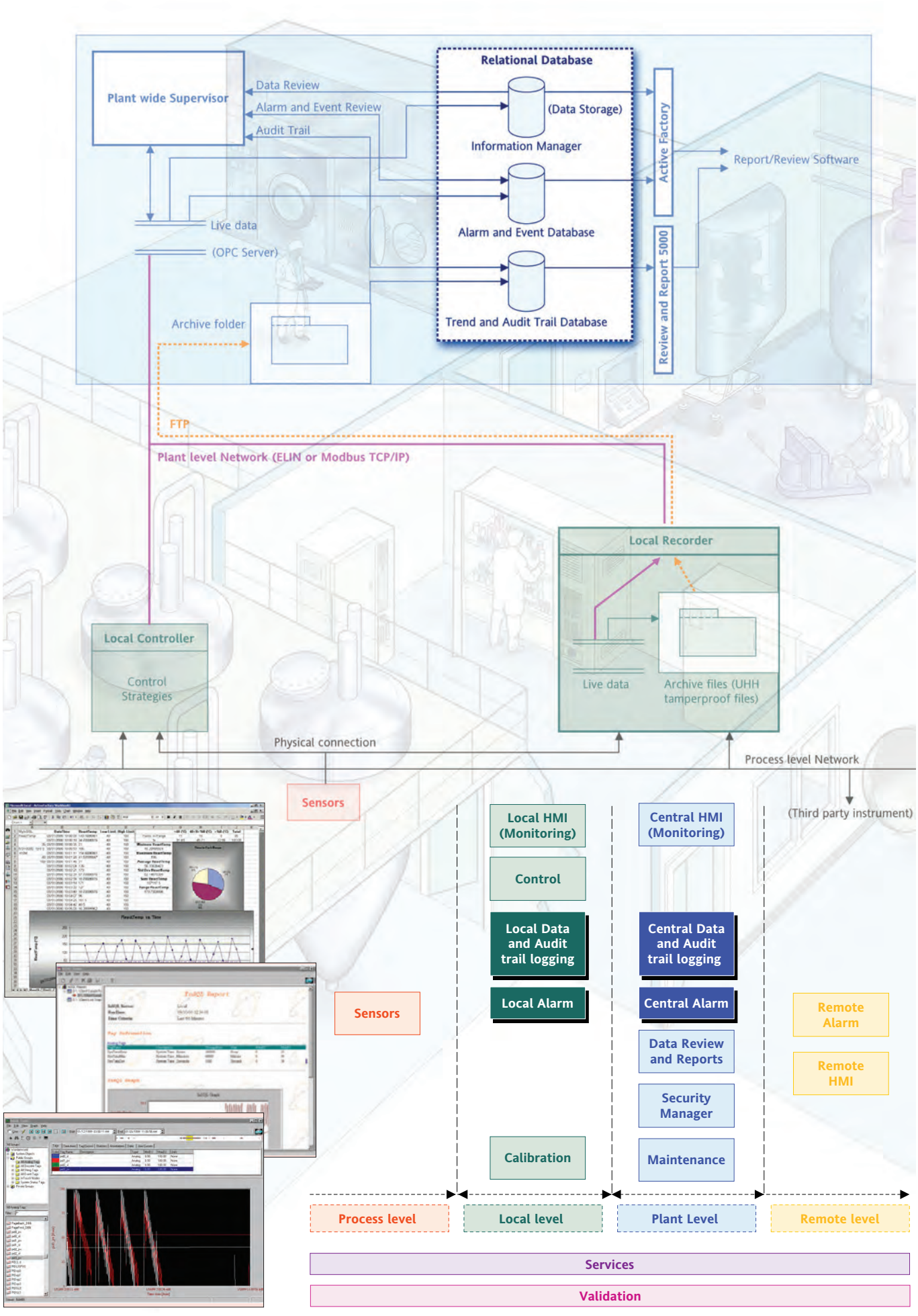
Alarms can be configured as critical, non-critical or as an event. Critical alarms will require manual acknowledgement and non-critical will be auto-acknowledged. Alarm selection and setpoint settings are available to the users with the appropriate access level and critical alarms can be configured to require an Electronic Signature for changes. Alarm acknowledgement and all changes to alarm settings are automatically logged as required by 21 CFR part 11.

All alarms and events are reported through local, central, and remote HMI panels. They are displayed in the Alarm Summary and Alarm History pages which provide a sort facility for the information. Alarms can be grouped by their criticality and function to ensure individual alarms can be quickly accessed.

Other features of the BMS/EMS alarm system include:

- Audible alarm notification
- Notification of alarm conditions to designated users on a designated telephone number
- Local printing of alarms and events



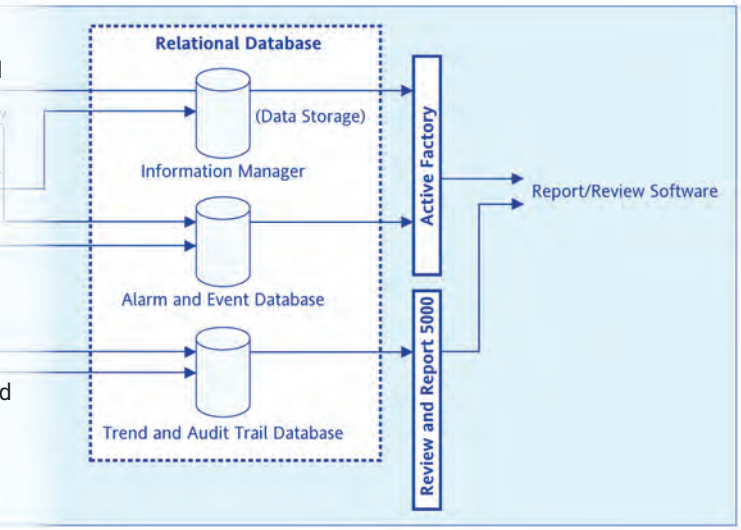

Plant wide Supervisor
Data Review
Alarm and Event Review
Audit Trail
Relational Database
(Data Storage)
Information Manager
Alarm and Event Database
Trend and Audit Trail Database
Active Factory
Review and Report 5000
Report/Review Software
Live data
(OPC Server)
Archive folder
FTP
Plant level Network (ELIN or Modbus TCP/IP)
Local Recorder
Live data
Archive files (UHH tamperproof files)
Local Controller
Control Strategies
Physical connection
Process level Network
(Third party instrument)
Sensors
Sensors
Local HMI (Monitoring)
Control
Local Data and Audit trail logging
Local Alarm
Central HMI (Monitoring)
Central Data and Audit trail logging
Central Alarm
Data Review and Reports
Security Manager
Maintenance
Calibration
Remote Alarm
Remote HMI
Process level
Local level
Plant Level
Remote level
Services
Validation

Easy to Use, Comprehensive Reporting

Review and Reporting

The BMS/EMS system provides a comprehensive review and reporting system. The system offers two methods for collecting data:

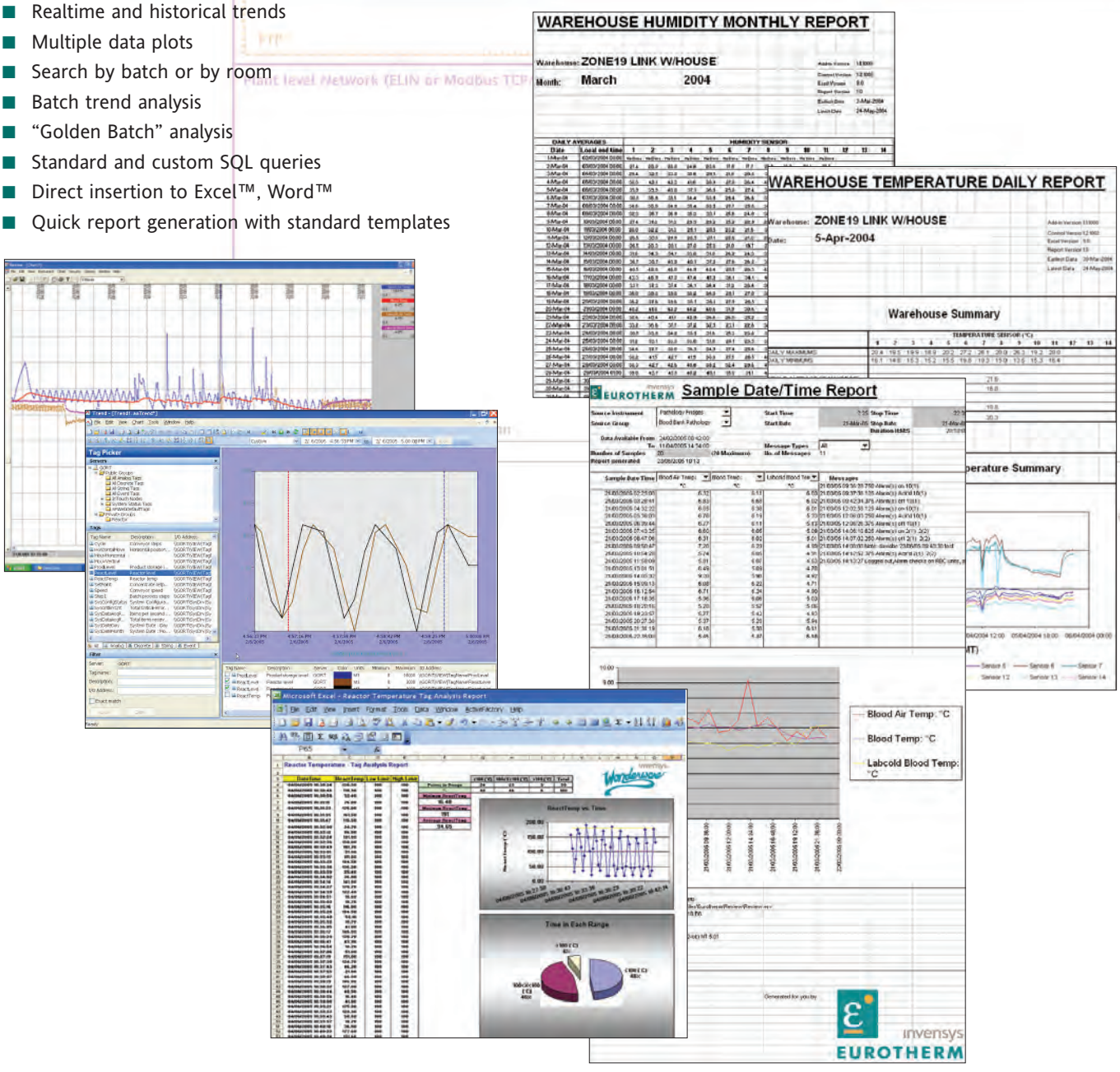
- Local data collection – Data collected locally in a secure format and archived centrally in a filing system
- Central data collection – Data collected in a central historical SQL relational database



These methods may be combined and, in both cases, the system provides the facility to create reports for individual rooms. A number of standard report templates are provided along with the facility for users to create their own reports.

Information can be automatically transferred and accessed from standard Microsoft® Office packages.

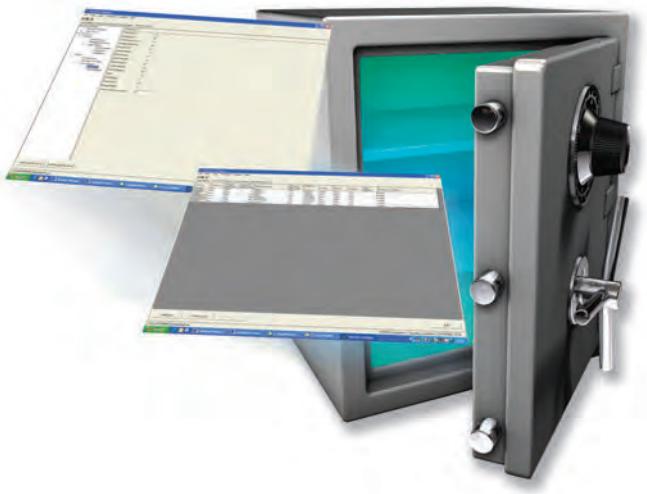
- Realtime and historical trends
- Multiple data plots
- Search by batch or by room
- Batch trend analysis
- "Golden Batch" analysis
- Standard and custom SQL queries
- Direct insertion to Excel™, Word™
- Quick report generation with standard templates



Easy to Operate at every Level

Security Manager

Security Manager offers significant operation cost savings and ease of use by allowing maintenance of user accounts and passwords from one or multiple locations. If a user needs to change their password they can do so on a local instrument or PC and this will be automatically distributed across all systems to which they have access.



- A common security tool across multiple product ranges
- Change in one place, deploy to many
- Support for multiple security zones
- Built-in audit trail for 21 CFR Part 11 validation
- Automatic version control
- Support for electronic signatures

Maintenance and Calibration

Maintenance is an essential part of any BMS/EMS system. Maintenance information on various elements of the system (e.g. last calibration date, calibration due date, last maintenance date, maintenance due date) is shown on multiple displays throughout the system. The system can provide warnings if calibration/maintenance dates for individual equipment are approaching and/or exceeded.

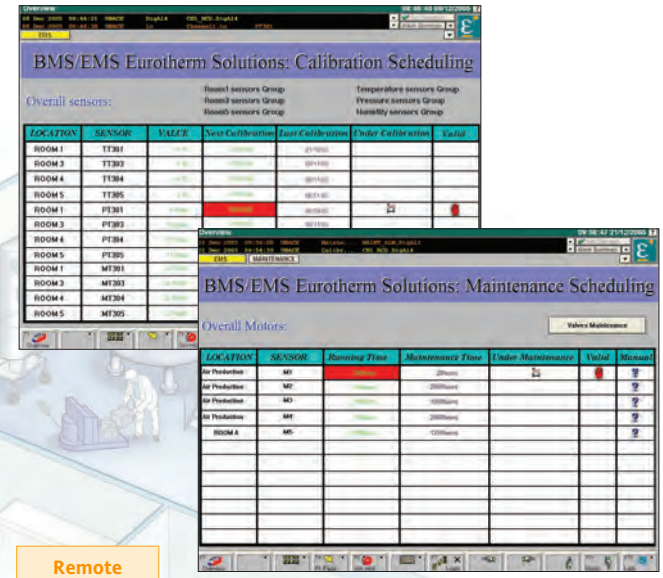
Access permission can be given to individual users to select maintenance modes for the following:

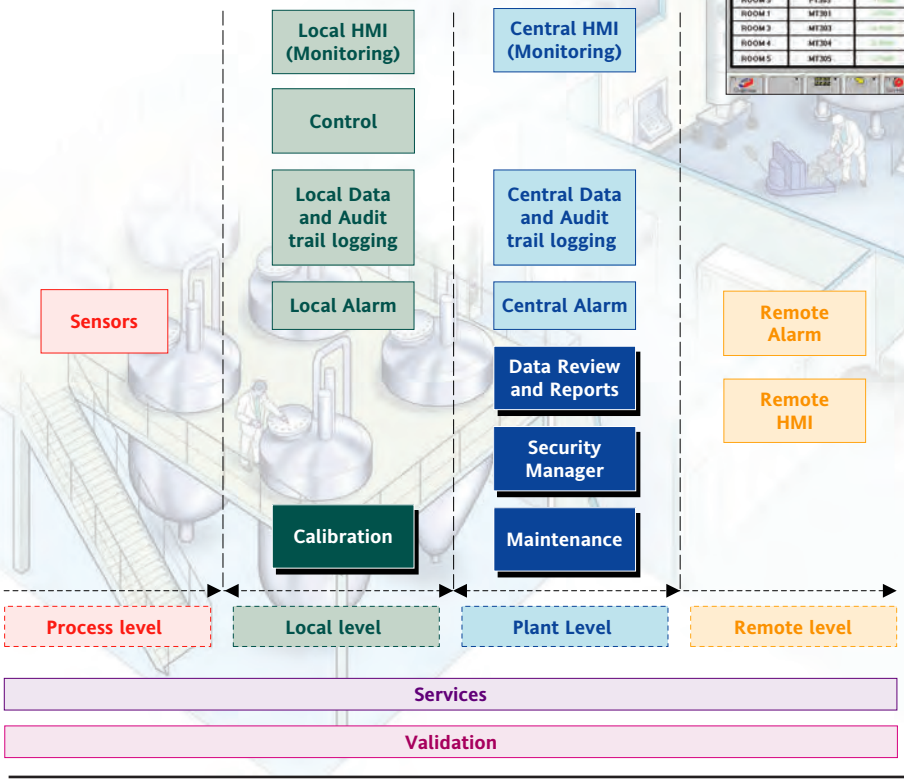
- Sensors
- Equipment (e.g. pumps, motors, valves)

Maintenance mode can also be selected for a given area e.g. a room or a zone of the plant.

While in maintenance mode the individual equipment or area will be clearly identified on the display using colour and text. The system can be set to suppress alarms and stop logging parameters for associated equipment at this time. Selection and the de-selection of the maintenance mode will be logged as an event in the audit trail.

Easy to use calibration tools are included in the system for use during maintenance mode. Selection and de-selection of the calibration mode is logged in the audit trail.





Total Lifecycle Support

Remote Alarm Notification

Nominated users can be quickly notified of alarm conditions via the telephone system. The system offers:

- Real-time alarm notification triggered from the plant system
- Ensured the delivery of the messages
- Easy to configure tools
- Login facilities and security patterns
- Redundancy options

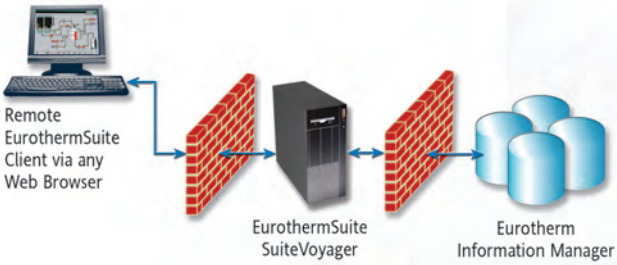
Services

Services need to be provided from the beginning of the project, through the project development and commissioning, and for the lifetime of the system. Eurotherm offers a complete range of services such as:

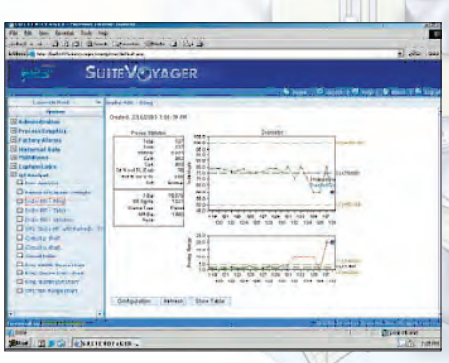
- Expertise to assist with the User Requirement Specification
- Project, Application and Validation engineering
- Commissioning (e.g. calibration) and qualification engineering
- Training courses covering products, control theory, validation etc.
- Helpdesk and on call services
- Product services

Remote Monitoring

Remote users, including off-site, can access plant information via a secure web portal.



- Remote real-time data visualisation
- Multi language facilities
- Support for multiple windows
- Integrated information from diverse data sources



Standard, Advanced Functionality

Validation

BMS/EMS

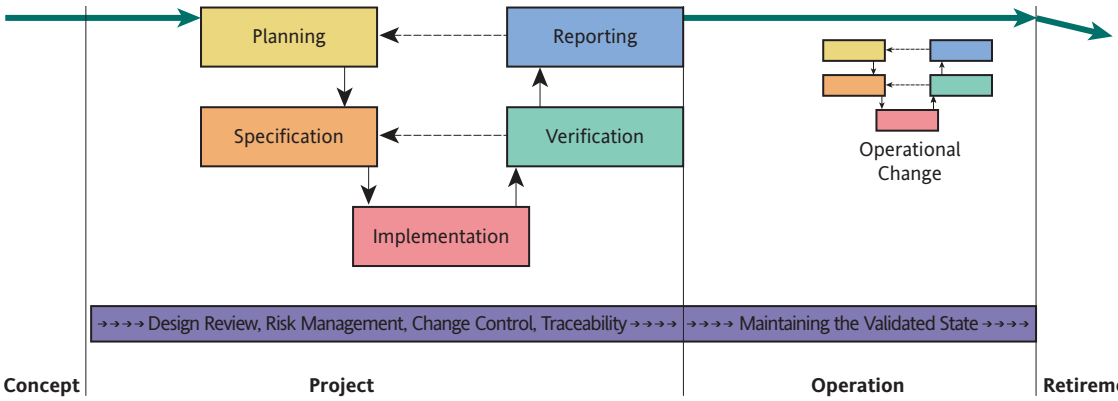
A key requirement for BMS/EMS solutions is validation. Where environmental conditions (e.g. temperature, humidity, differential pressure, air flow, sterility, containment) have a direct impact on product purity, safety, quality or efficacy they need to be monitored against predetermined limits and logged. In this case the BMS/EMS system used for collecting and logging the data needs to be validated. According to ISPE guidelines, it is good practice to monitor the performance of equipment such as fans, coil and control components, but it is not a regulatory requirement.

Documentation

Validation documentation needs to be provided through the life cycle of the BMS/EMS system. Eurotherm can offer a range of documentation services following GAMP guidelines and in accordance with customer requirements:

- User Requirement Specification
- Functional Specification
- Design Specification
- Hardware Testing
- Code Review
- Factory Acceptance Test
- Installation Qualification
- Operational Qualification
- Periodic review

GAMP LIFECYCLE



Mean Kinetic Temperature (MKT) Calculation

Measurement and recording of temperatures is vital to the storage of perishable goods, but there is more than one way to record an average.

The ICH defines the mean kinetic temperature as being *"A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period"*.

MKT expresses the cumulative thermal stress experienced by a product at varying temperatures during storage and distribution. It differs from other means (such as a simple numerical average or arithmetic mean) in that higher temperatures are given greater weight in computing the average, recognising the accelerated rate of thermal degradation of materials at higher temperatures.

$$T_k = \frac{\frac{\Delta H}{R}}{\ln\left[\frac{e^{\frac{-\Delta H}{RT_1}} + \cdots e^{\frac{-\Delta H}{RT_n}}}{n}\right]}$$

T_k – the mean kinetic temperature in K
ΔH – the heat of activation, 83.144kJ.mole^{-1}
R – the universal gas constant, 8.3144x10-3kj.mole^{-1} .k^{-1}
T_1 – the daily average temperature (K) day 1
T_n – the daily average temperature (K) day n
n – the total days in the calculation

The mean kinetic temperature is calculated as being:

There are a number of interpretations of how this calculation is achieved using real samples:

- All sample values fed into formula
- Maximum/minimum samples fed into formula separately (recommended by the FDA)
- Arithmetic mean of maximum and minimum fed into formula (recommended in the US Pharmacopeia and by the UK MHRA)

Eurotherm minimises the implementation and operation cost of providing MKT data by making all of the above methods as integral part of our solution with:

- A choice of stability testing period (hourly / daily / weekly)
- A choice of sampling frequency (from 1 minute to 1 hour)
- Option to remove individual probes from the calculation (e.g. during a calibration process)
- Corrective action in case stability is out of specification
- Secure and low cost custom reporting

Life Sciences

INDUSTRY

- **Secure electronic data**
- **Self healing data archiving**
- **Dynamic reporting**

Environmental Quality Monitoring System

Application Note

... with data security and "Store & Forward"

Eurotherm 21CFR Part 11 Compliant Data Files with Direct SQL Interface supporting true "Store & Forward" technology

21CFR Part 11 Compliance

Eurotherm proprietary tamperproof data files are generated in a binary, compressed and check- summed format. To assist data integrity the standard Eurotherm visualisation tools reject invalid / altered (incorrectly check-summed) records.

Audited Data

Auditor features on Eurotherm products have been specifically designed to meet the requirements of the FDA 21CFR Part 11 document for Electronic Records and Electronic Signatures. Data is held in both Human Readable and Electronic form. Electronic data can be viewed, analysed and printed off-line using the secure Review package.

The Auditor, besides logging process values, provides secure, product generated, Audit trails. The Audit trail records all actions taken by the operators.

Direct SQL interface

Eurotherm data files are identified with .uhh suffix. These files meet the stringent requirements of regulatory bodies such as the FDA, EMEA, MHRA etc. However with the advent of Electronic Batch Records there is a need for a more open data structure. As always the Eurotherm approach to problems such as these results in a complete solution that meets all user and regulatory expectations. The '.uhh' files now have a direct SQL interface that is achieved through a series of 'Stored Procedures'. The result of this approach is to:

- Retain the original data integrity for 21CFR Part 11 compliance
- Operate as a high speed data provider through 'Stored Procedure' queries
- Provide a direct interface to any SQL based historian
- Regular automatic update of SQL database, "forward procedure"
- Opens the data search engine to provide a more comprehensive query subset
- Ensure full 'Store & Forward' support direct from the sensor level

Application Notes

Environmental Quality Monitoring System

Pharmaceutical Environmental Quality Monitoring System

Control and monitoring of storage and production environments are very important within the Pharmaceutical Industry. The FDA, MHRA, EMEA and other regulatory bodies require accurate measurement and storage of environmental parameters and, if the storage medium is electronic, the methods used must comply with 21 CFR Part 11.

Data Logging

Data logging is a key requirement for EMS systems. **21 CFR Part 11 requires that logged data will be tamper proof and will include critical environmental parameters** (temperature, humidity, pressure, particulate sizes, etc), with audit trails including:

- Accurate time and date stamps
- Alarms and events
- User actions and details (e.g. setpoint changes)
- User notes
- Electronic Signatures
- Login / Logout

Eurotherm® EMS systems log plant data to tamper proof files and SQL relational databases. Data logging can be offered as:

- **Local logging**
  (Tamper proof file with direct SQL interface)
- **Central logging**
  (SQL database)
- **Local and central logging**
  (Tamper proof files and SQL database)

The availability of logged data can be significantly increased by the local and central logging option. This allows data collection in multiple devices to further protect vital plant data.

Time synchronisation is included to ensure accurate time and date stamps, as required by 21 CFR Part 11, to a known clock source.

The EMS system offers provisions for electronically copying data for archive and export facility to common packages (e.g. Excel, Word, PDF, etc.) for viewing of secure records in human readable format.

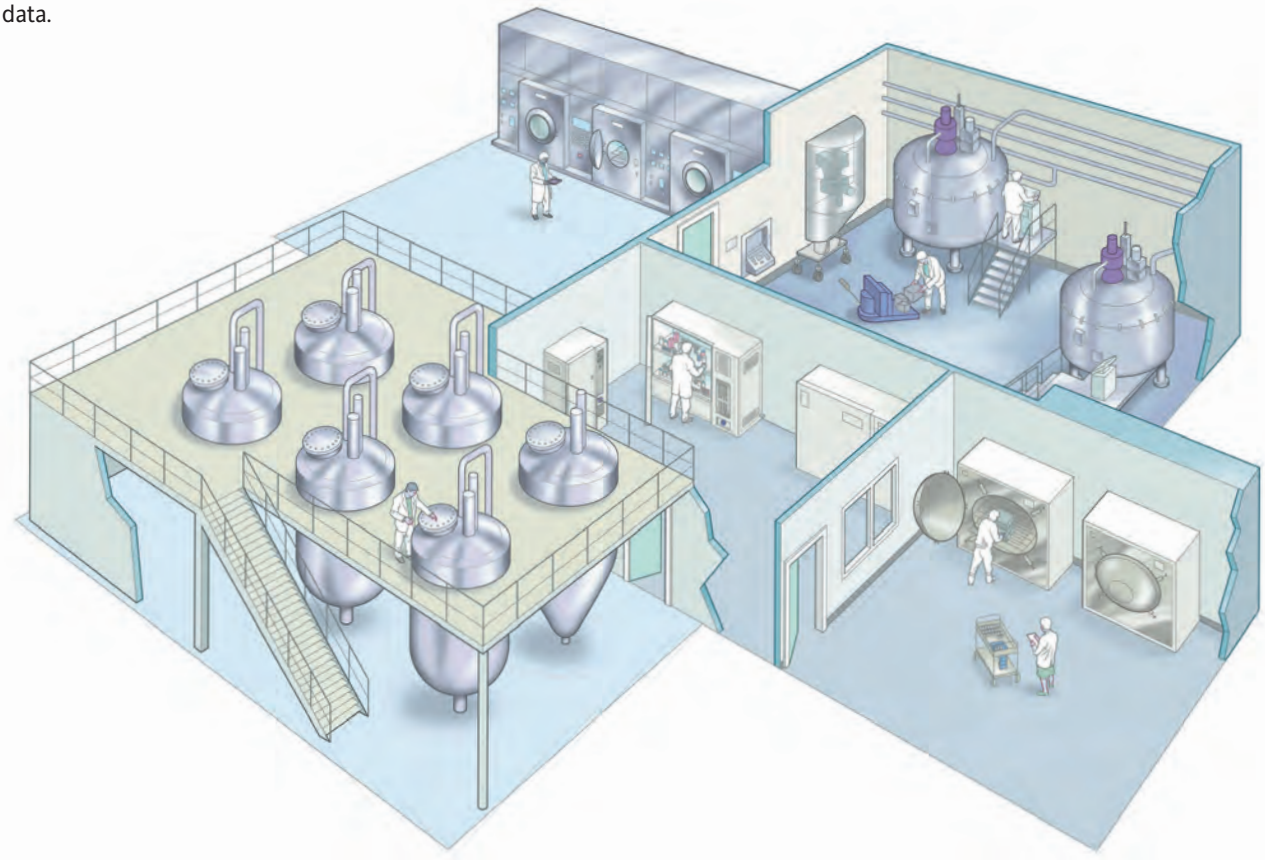
In addition the proprietory tamper proof files, Eurotherm EMS offers a direct SQL interface that facilitates easy integration to other data historians.

Other features of the system include:

- Power and network recovery automatic procedures
- FTP protocol to transfer to central server
- Scheduled transfers

The system can be configured to provide logging for non-critical parameters including:

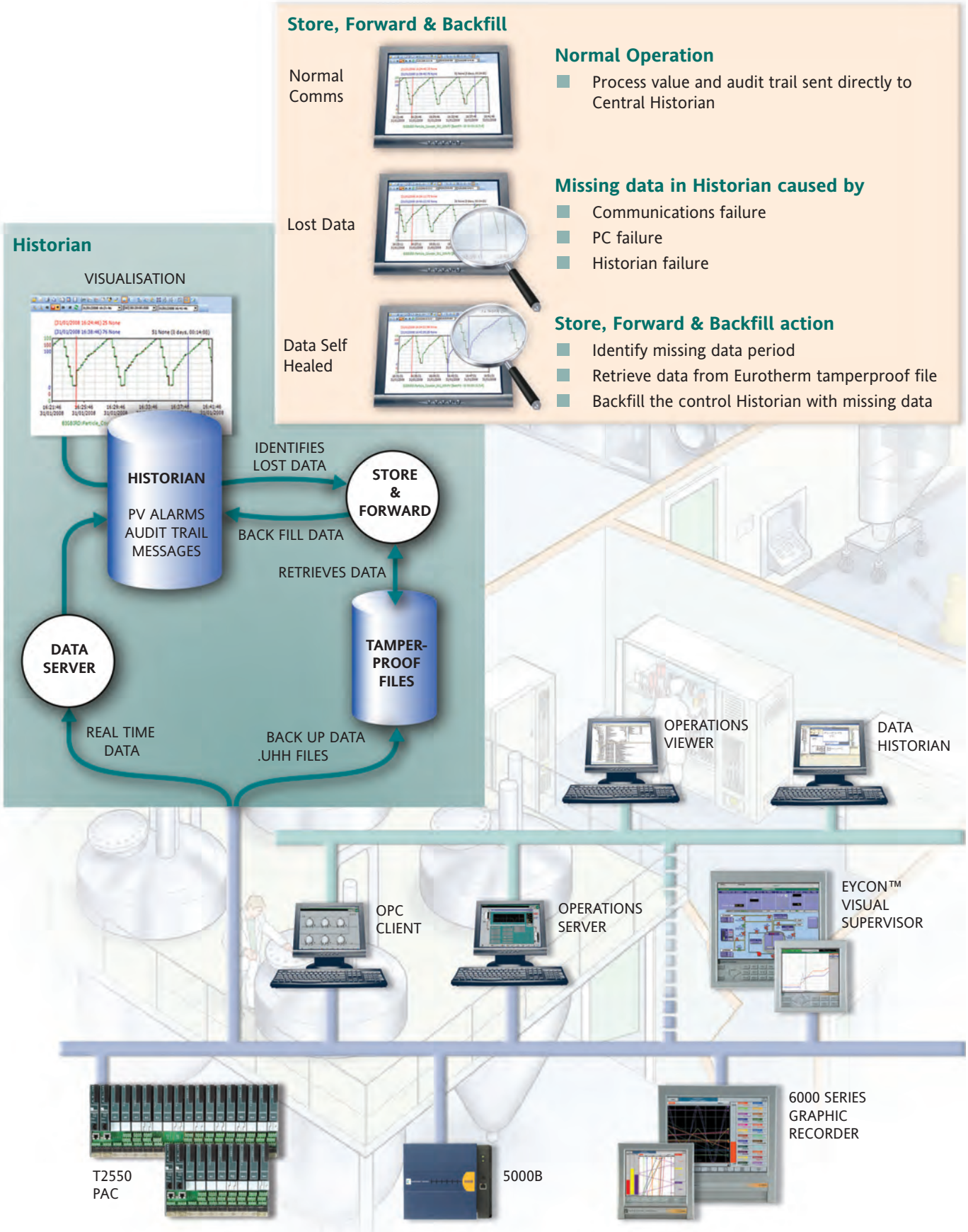
- System events
- Equipment failure
- Equipment performance and maintenance
- Energy usage



Self Healing Data Archiving with “Store & Forward”

‘Store & Forward’ is a self healing 21 CFR Part 11 data archiving system that continuously stores data locally and is regularly forwarded to the configured server. This data is therefore available to update a historian package.

This results in secure electronic recording with total data integrity.



Secure Electronic Data

In addition to meeting the exacting requirements of generating regulatory (FDA, EMEA, etc) compliant records, Eurotherm solutions provide significant benefits by including redundant logging with “Store & Forward” security. This ensures that data integrity is maintained through the implementation of fault tolerant features.

Logging parameters

Regular Time Based Process Variable
(Actual max, min, average)

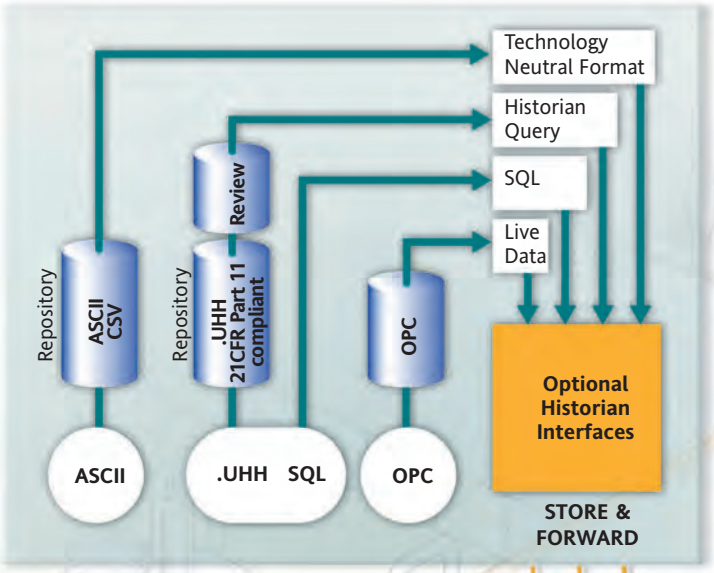
For example:

- Temp
- Pressure
- Particle count
- Relative Humidity
- Speed
- Door Status

... plus any other process parameter

Event Based

- Channel Alarms
- User event messages
- Operator notes
- Log in/log out
- Batch start/stop
- Operator actions
- Electronic signatures



Logging options

Event Based

- Continuous trace
- Batch
  - Start/stop
  - Continuous (Sub phases or sub batches)
- 21 CFR Part 11 Compliant
- Signed audit trails

Data Presentation

- Trend chart and spreadsheet based
- Absolute or relative time
- Batch or Sub Batch data search by:
  - Absolute date & time
  - Relative date & time
  - Batch name
  - Sub Batch name
  - Audit Trail

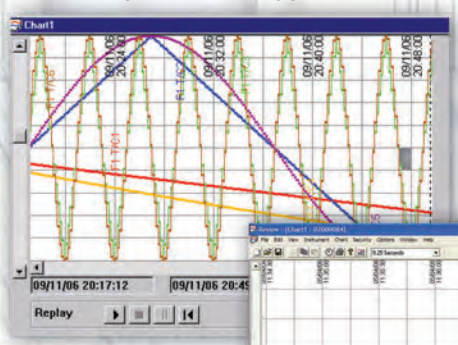
Secure Batch Release

- Operator signed and authorised batch and continuous records
  - Reviewed
  - Approved
  - Released

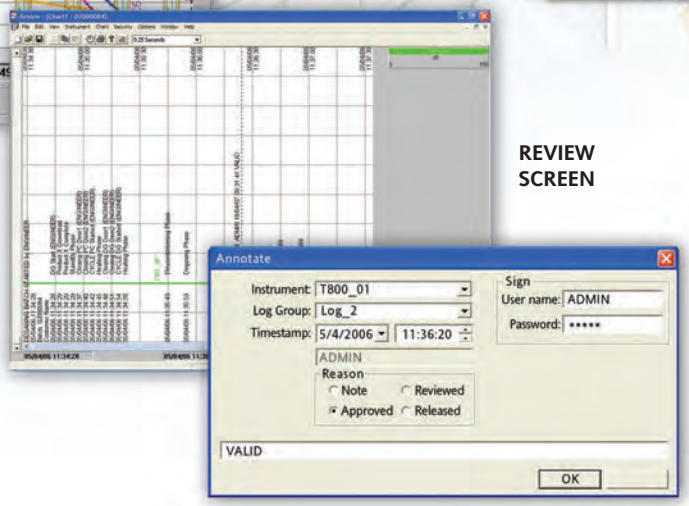
Data Security

- 21 CFR Part 11 compliant binary encoded read-only files
- Auto-archive to nominated server
- Secure embedded audit trails
- Electronic signing and authorising

CHART REPLAY SCREEN



REVIEW SCREEN



BATCH APPROVAL SCREEN

Redundant OPC Servers

Redundant Data Acquisition at Local Level

OPERATIONS VIEWER

DATA HISTORIAN

Ethernet

EYCON™ VISUAL SUPERVISOR

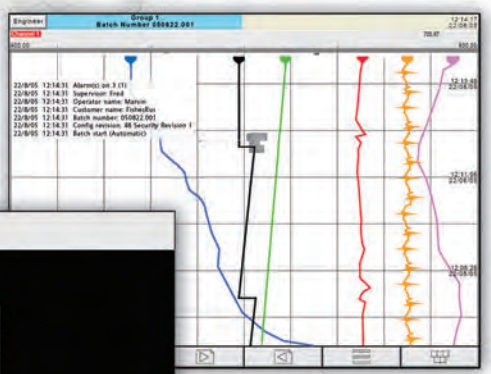
OPERATIONS SERVER

Ethernet

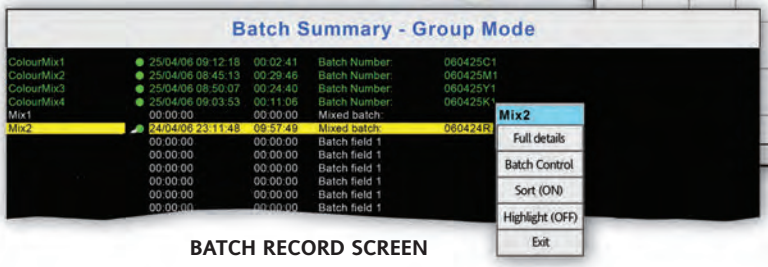
INDUSTRY STANDARD PLC

5000B

6000 SERIES GRAPHIC RECORDER



BATCH RECORDED DATA SCREEN



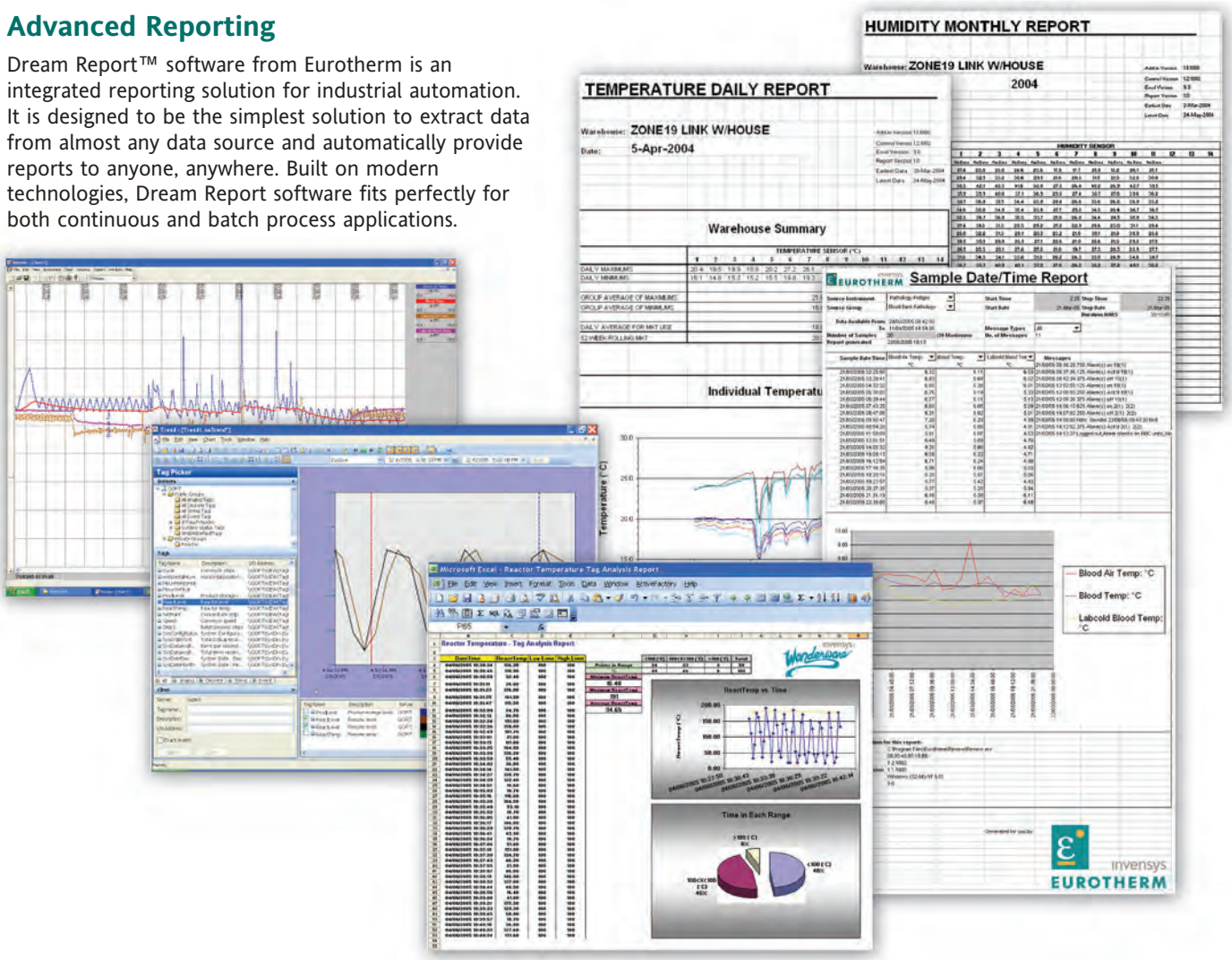
BATCH RECORD SCREEN

Dynamic Reporting

Eurotherm offers a range of reporting utilities to generate reports automatically or on demand. For each report utility users will be able to use the standard library report or create their own custom reports

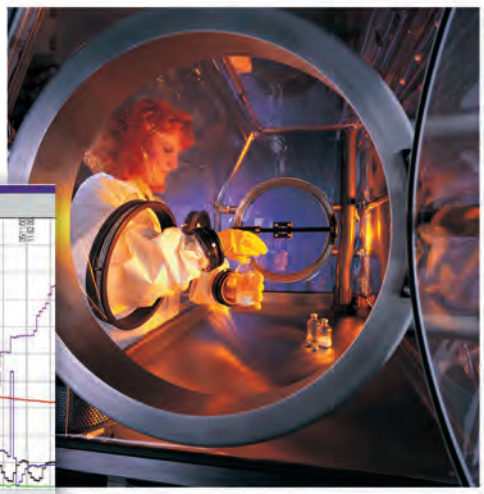
Advanced Reporting

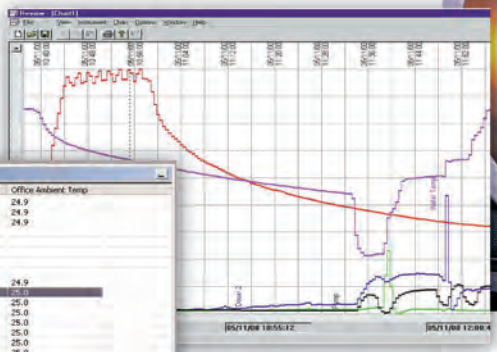
Dream Report™ software from Eurotherm is an integrated reporting solution for industrial automation. It is designed to be the simplest solution to extract data from almost any data source and automatically provide reports to anyone, anywhere. Built on modern technologies, Dream Report software fits perfectly for both continuous and batch process applications.

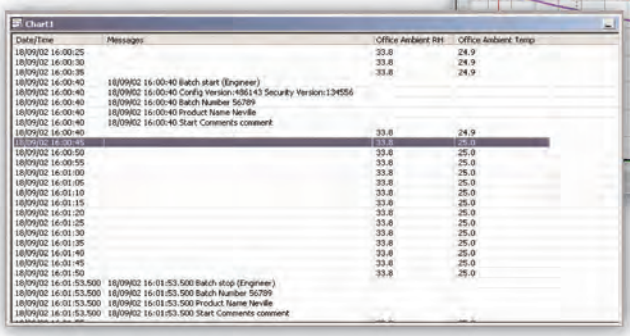


Standard Reporting

Eurotherm Review is a PC based Software package that allows the display and printing of archived data files from the Eurotherm range of Data Acquisition units. Archived Data files can be transferred to the Review database in one or more ways, either by using a network connection or reading directly from the units' removable media. Once transferred the data can be used to recreate the charts, and spreadsheets for viewing and if necessary printing.







Data Management, Acquisition and Control Products

Supervisory System – EurothermSuite Operations Server/Viewer: provides a single integrated view of your system. The software enables the engineers, supervisors, managers and operators to view and communicate with the workings of your entire operation through graphical representations of your production process. The software provides a host of features including distributed alarm handling, distributed historical data, centralised alarm printing, etc.

- Satisfies 21CFR Part 11 requirement
- Engineered displays tailored to meet the needs of BMS/EMS
- System wide availability of information
- Client Server architecture with master/backup servers
- Uses Wonderware InTouch

Historian – Information Manager: combines the power and flexibility of a relational database with the speed and compression of a real time historian package. The information manager is up to 300 times faster than a conventional relational database but only uses 2% of the disk space normally required by a conventional relational database.

- Satisfies 21CFR Part 11 requirement
- Captures and stores all EMS data
- Realtime and historical data can be made available to enterprise
- Minimises storage space and controls volume of data retrieved
- Uses Wonderware Historian

T2550 Programmable Automation Controller: offers DDC functionality and much more while being extremely cost effective. Capable of continuous analog, logic and sequential control, and redundant 21CFR Part 11 logging is designed to address all the needs of your BMS/EMS

- Satisfies 21CFR Part 11 for electronic records
- Cost effective redundancy
- REDUNDANT LOGGING
- Continuous and sequential control
- Hot swap I/O
- Alarm handling
- Wide range of I/O: PRT, TC, 4-20mA, 0-10V, mV, etc.

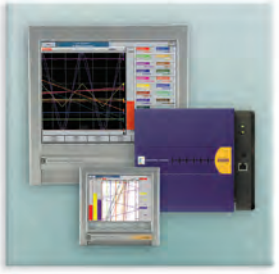
Eurotherm Eycon™ Visual Supervisor: provide innovative, multi-function control, recording and visualisation – bringing Eurotherm's expertise in control, data acquisition and process automation into a single process management unit.

- Satisfies 21CFR Part 11 requirement
- Logging with "Store & Forward"
- Accurate continuous and sequential control
- Alarm handling
- Communications including Modbus, Modbus TCP, OPC, Profibus

Recorders: adaptable functionality incorporated into the 6000A instruments will meet the most demanding of solution requirements. With their ease of use and configuration, you can be sure to maximise your return on investment.

- Satisfies 21CFR Part 11 requirement
- Multiple logging media
- Remote viewing with Bridge
- Maths function

Similarly the 5000B is a versatile solution for back of panel or wall mounting solutions where local visualisation is not required.



Sensors: communicate measurement and status information from the process to the control and monitoring modules of the EMS system.

Sensors supported by Eurotherm solutions include:

- Temperature
- Luminescence (light level)
- Gas Level
- HVAC healthy status
- Relative humidity
- Particle counter
- Air pressure or differential pressures
- and many others

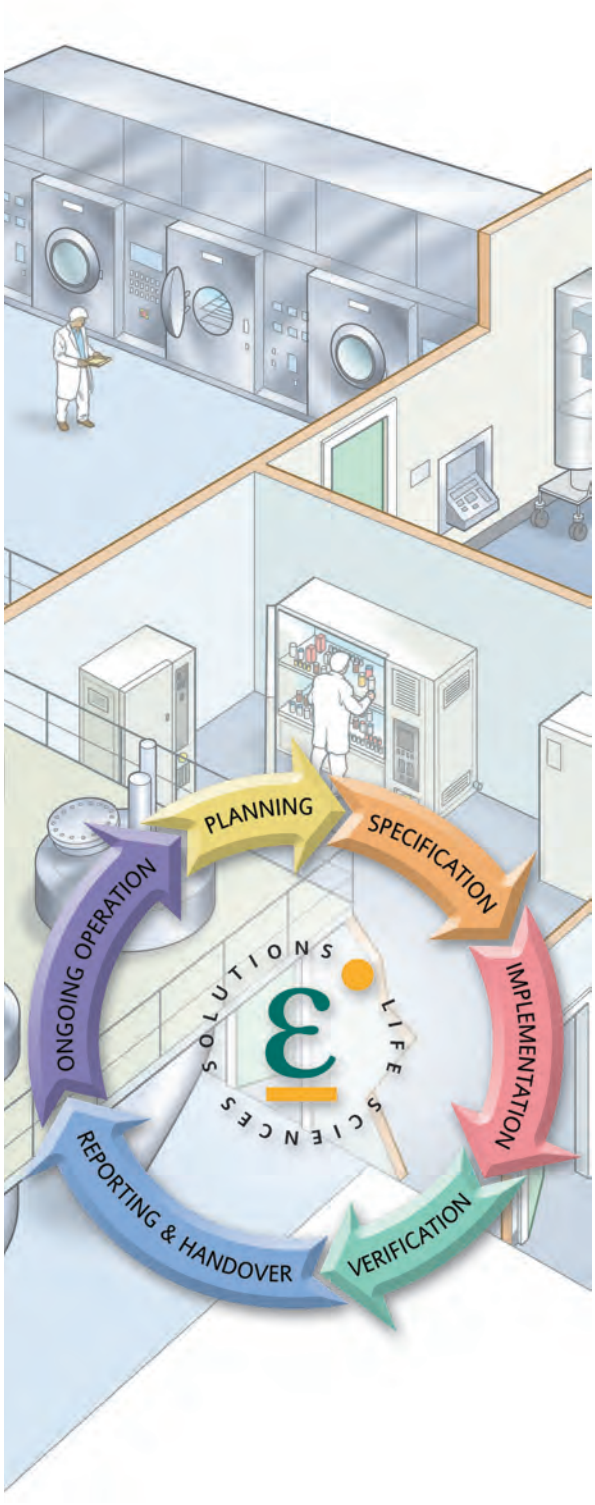
Life Sciences CATALOGUE

REGULATIONS 1

GAMP

- Eurotherm and Pharmaceutical Project Lifecycle
- Quality and Project Plan

Appendix 1 and 2 include reprints from some of the applicable 21 CFR's and Guidance documents.



Eurotherm and the Pharmaceutical Project Lifecycle

Eurotherm's Quality Management System is approved by Lloyd's Register Quality Assurance to ISO9001:2000 and the TickIT guide Issue 5

Many of our pharmaceutical, biotechnology and medical devices customers request work to the GAMP Guide for Validation of Automated Systems - guidelines which have become the de facto standard for Good Automated Manufacturing Practice in the healthcare industries.

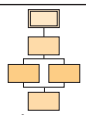
This document summarises the assistance Eurotherm can offer with validation activities throughout your project lifecycle. Eurotherm has a long history of projects successfully validated to GAMP guidelines including many which are now operating in FDA regulated environments.

Hardware and Software Categories

GAMP5 recognises that the risk associated with a hardware or software element is related to the level of 'bespokeness' (for example a PID lop created from a mature library module is much more likely to work first time than one implemented from scratch in C++). Hardware and software categories are defined as below and used to determine the appropriate level of validation.

Software Categories

(Note the GAMP4 categories 2 and 3 both now fall within GAMP5 category 3)

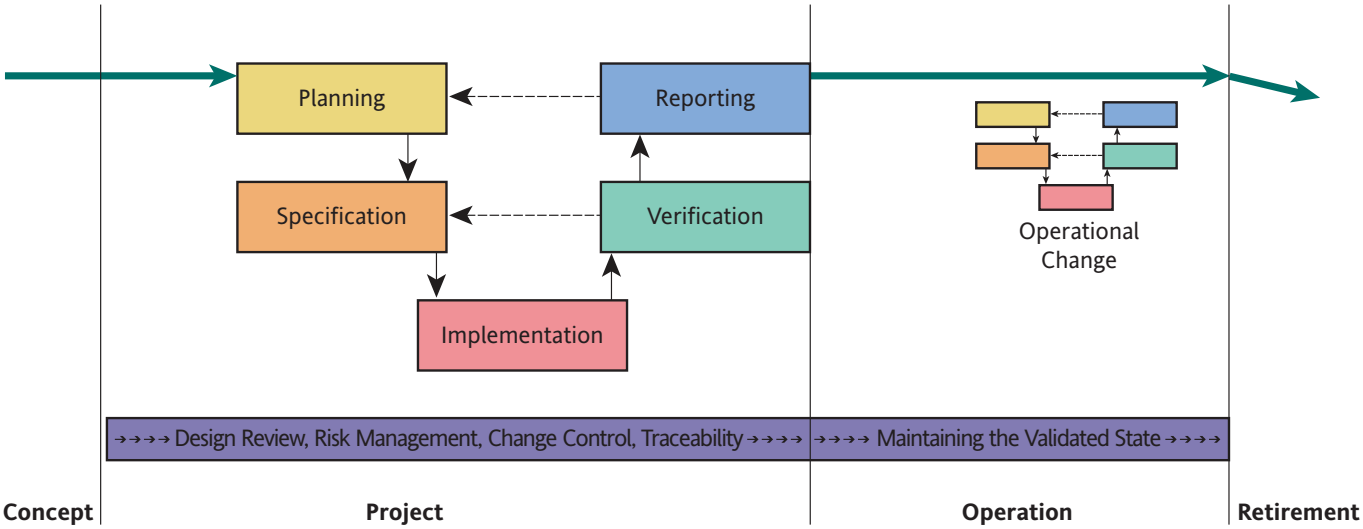
Category	Software Type	Example	Validation Approach
1	Infrastructure Software	Microsoft Windows NT Workstation	Record version, verify correct installation by following approved installation procedures (refer to IT Infrastructure Good Practice guide).
3	Non Configured (may have runtime parameters saved and stored)		Abbreviated lifecycle approach. URS. Risk based approach to supplier assessment. Record version number, verify correct operation Risk-based tests against requirements as dictated by use. Procedures in place for maintaining compliance and fitness for intended use.
4	Configured	EUROTHERM suite	Lifecycle approach. Risk based approach to supplier assessment. Demonstrate supplier has adequate QMS. Some lifecycle documents may be retained by supplier only. Record version, verify correct installation. Risk based testing to demonstrate application works as designed within the business system. Procedures in place for maintaining compliance and fitness for intended use. Procedures in place for managing data.
5	Custom Software	 LINtools sequence	Same as category 4 plus: More rigorous supplier assessment. Possession of full lifecycle documentation by end user. Design and source code reviews.

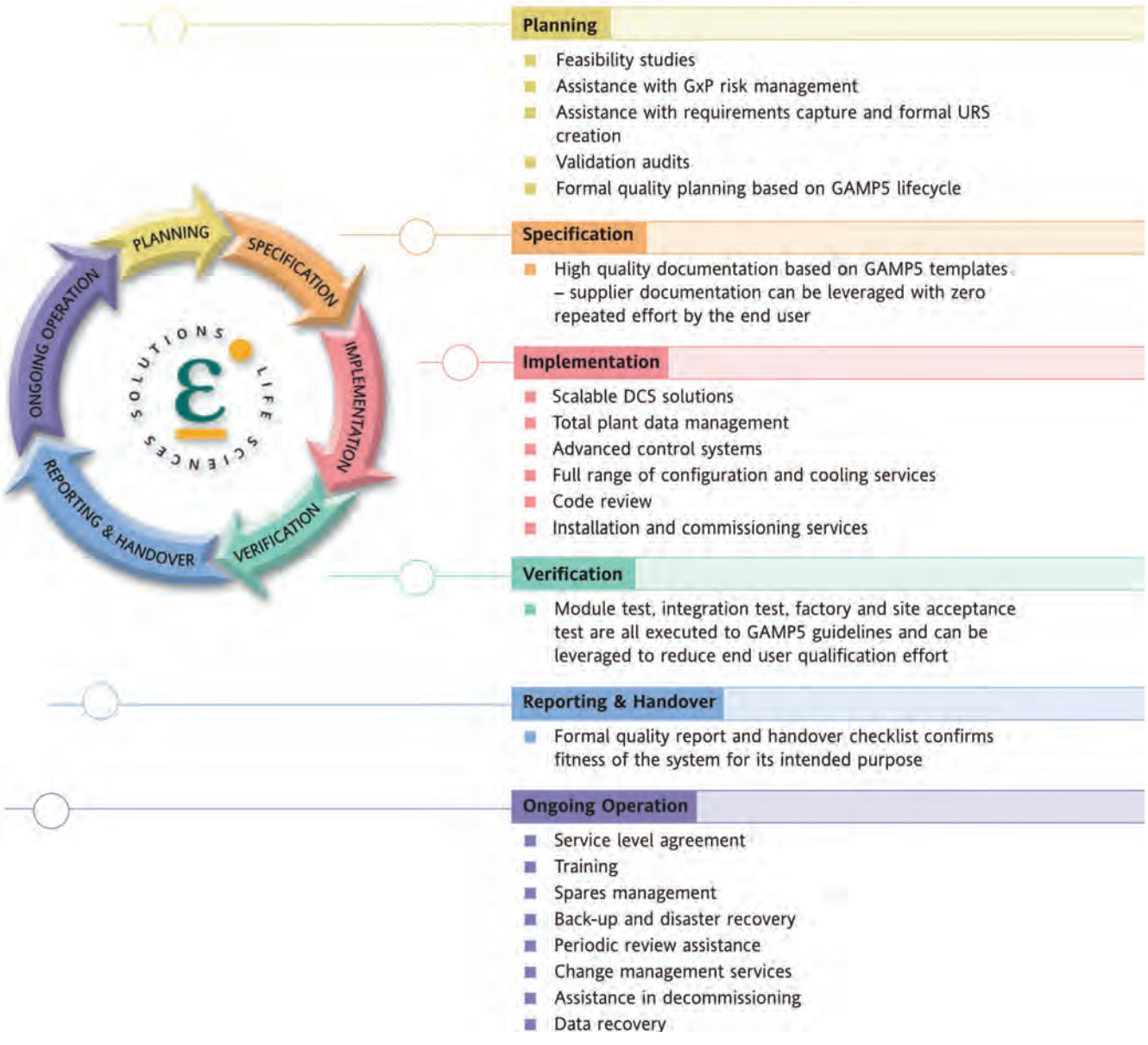
Hardware Categories

Category	Hardware Type	Validation Approach
1	Standard Hardware Components	Record model version, serial number. Verify correct installation/connection.Apply change control
2	Custom Built Hardware Components	As for standard components but also require a design specification and acceptance test. Supplier may be audited

GAMP Lifecycle

The 'overall GAMP5 lifecycle and be summarised as follows, with the rigour of activities within each phase depending on the GxP risk associated with the system.





Eurotherm Lifecycle Services

Planning

Hosting of Supplier Audit

Eurotherm is always happy to host supplier audits prior to placement of an order. A recent supplier audit concluded: *"Eurotherm were able to demonstrate a good working knowledge of both the GAMP and FDA requirements. The project file reviewed as part of this audit highlighted their ability to adhere to the regulated guidelines"*

Specification

Generation of Quality Plan

The quality requirements stated in the customer's validation plan and user requirement specification are used to develop a supplier quality plan to GAMP5 Appendix M6. The document covers quality planning, project planning and change control (to GAMP5 Appendix M8) and configuration management (to GAMP5 appendix M9) procedures.

Generation of Functional Specification

The functional requirements outlined in the customer's user requirement specification are used to develop a functional specification to GAMP5 Appendix D2. The document covers functions to be performed, data requirements, interfaces and non-functional attributes such as availability and maintainability. A traceability matrix cross-references each function back to the user requirements.

Generation of Factory Acceptance Test Specification

A factory acceptance test specification is prepared to GAMP5 Appendix D6. This sets out testing procedures and the test set-up to be used as well as actual test scripts. A traceability matrix cross-references each test back to the functional specification and hence the user requirements.

Generation of Hardware Design Specification

A hardware design specification to GAMP5 Appendix D3 includes a full drawing package plus details of computer systems, instruments, I/O systems to be supplied. Details of environment and required supplies are included.

Generation of Hardware Test Specification

The hardware test specification to GAMP4 Appendix D6 covers hardware visual checks, power up and diagnostic checks.

Generation of Software Module Specifications

For each Category 5 software item, a module specification is prepared to GAMP5 Appendix D4

Generation of Software Module Test Specifications

For each Category 5 software item, a module test specification is prepared to GAMP5 Appendix D6

Generation of IQ Specification

The IQ specification to GAMP4 Appendix D6 covers hardware visual checks, power up and diagnostic checks to be performed in order to confirm correct installation on site.

Generation of OQ Specification

The OQ specification to GAMP5 Appendix D6 covers functional and interface tests to be performed in order to confirm correct operation of the system.

Production of Software

Software is produced to GAMP5 Appendix D5. Formal peer review of code is carried out for each Category 5 item.

Production of Hardware

Eurotherm's ISO9001 procedures cover manufacture of Eurotherm products, purchase of bought-out hardware and integration of both into standard or custom enclosures.

Implementation

Installation

Eurotherm can offer installation assistance as required.

Installation Qualification

IQ against the approved specification is carried out by a Eurotherm engineer, witnessed by the customer to confirm correct installation of the system.

Operational Qualification

OQ against the approved specification is carried out by Eurotherm engineers and customer together to confirm correct operation of the system.

Performance Qualification

Eurotherm can offer site assistance during the process qualification.

Validation Report

Although the validation report is the responsibility of the customer, results from each stage of testing are designed to be easily 'pulled in' as evidence of phase completion. Tabular appendices are provided for test progress and faults raised.

Verification

Hardware Acceptance Test

The customer is invited to witness hardware acceptance to the approved test specification.

Software Module Test

For each Category 5 software item, a module test is carried out to the approved test specification.

System Integration

Hardware and software are integrated into a complete system.

Integrated Test

Eurotherm engineers run through all the tests in the factory acceptance test specification prior to inviting the customer witness the tests.

Reporting & Handover

Factory Acceptance Test

The customer is invited to witness functional testing to the approved test specification.

Ongoing Operatoin

Service Level Agreements

Service level agreements to GAMP5 Appendix O2 are available for a range of different cover levels.

Eurotherm Ltd.
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Durrington
Worthing BN13 3PL
United Kingdom

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F +44 (0)1903 265982
E info@eurotherm.co.uk
www.eurotherm.co.uk

Title	Double-click HERE and type Project Title
Customer	Double-click HERE and type Customer Name
Eurotherm Reference	Double-click HERE and type Eurotherm Reference
Customer Reference	Double-click HERE and type Customer Reference

Explanatory note (delete this before publication):
1) enter all fields above plus date and issue number below
2) search for 'TBA' to find items which need entering on a per-project basis.
3) if not based in the UK, replace the header with the appropriate one from your local letterhead

QUALITY & PROJECT PLAN

Prepared by	..... Sign / Date	..... Printed Name	..... Title
Quality Review by (Eurotherm)	..... Sign / Date	..... Printed Name	..... Title
Quality Approval by (Customer) Approved for use as Basis for Project Activities	..... Sign / Date	..... Printed Name	..... Title
Issue	Enter Issue No		
Date	Enter Date		

CONTROLLED CIRCULATION		
Copy	Issued to	**This Copy**
Master	Double-click HERE and type Customer Name	
Copy 1	Project File	

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1. DOCUMENTATION RECORDS

TEMPLATE DETAILS			
HISTORY:			
T1	Template document written to accompany Eurotherm systems engineering procedure SEP013 issue 1. Explanatory notes added in italics.		03 Jul 2003
T2	Template updated following re-issue of Eurotherm System Engineering Procedures in form suitable for use across all group companies. SEP013 now SEP109.		25 Jan 2006
T3	Template updated for GAMP5		27 May 2008
APPROVAL DETAILS FOR CURRENT TEMPLATE			
Template prepared by	Karen Ashworth	Validation Officer	27 May 2008
Template reviewed for Technical Content	Malek Madani	Technical Manager	27 May 2008
Template reviewed for Quality Assurance	Martin Greenhalgh	Global Quality Manager	27 May 2008

DOCUMENT REVISION HISTORY		
Issue	Detail	Issue Date
1a	Project version 1 developed from template T3 and issued for internal review	TBA Enter Issue Date

TBA Explanatory note (delete this before publication):
Once internal review is complete, an additional entry needs to be made for version 1 saying something like 'Internal review comments included. Document issued for customer approval'
All subsequent issues (eg version 2) need to detail the changes which have been made including the section reference and the reason for the change (eg ref to customer comment). When creating a new version: accept all previously tracked comments; make changes with change tracking enabled; hide mark-up (in the VIEW menu) before printing or issuing the document.

2. INTRODUCTION

TBA: Explanatory note (delete this before publication): The quality plan is Eurotherm's response to the customer's quality requirements (in the same way that a functional specification is the response to the customer's functional requirements). It is a key document in defining the project lifecycle. It allows agreement of which procedures (Eurotherm, customer, GAMP,...) will be used to control and document each project activity. It is often extremely helpful to discuss a draft version during the bid process in order to make sure that Eurotherm and customer expectations (eg with regard to documentation deliverables and site testing requirements) are agreed.

2.1 Purpose

A Quality Plan is a key document in defining the project lifecycle. It sets out the proposed method of meeting the customer quality requirements and allows agreement of the controlling procedures for each project activity.

2.2 Scope

This document defines the method for meeting customer quality requirements on the control system required by Double-click HERE and type Customer Name for their Double-click HERE and type Project Title Project.

2.3 Contractual Status

This document, once approved, provides the basis for project implementation. On project completion, this document passes to the customer for archiving.

2.4 Relationship to Other Documents

2.4.1 Applicable Standards

This document has been written to meet the guideline for quality and project planning contained in GAMP5 A Risk-Based Approach to Compliant GxP Computerized Systems Appendix M6.

2.4.2 Relationship to Customer Validation Requirements

TBA: Explanatory note (delete this before publication): The validation requirements may be in the URS or may be in a separate validation plan. Include references here to the relevant document(s). It is normal to include version numbers for these base documents for contractual reasons, though this may be worth exploring with the customer as it means an update of the quality plan if the customer issues a new URS/VP in order to keep it up to date with changes resulting from design reviews or risk assessments.

The customer quality requirements in this document are derived from the lifecycle attributes listed in the following documents:

Project / Document Ref	
Title	
Issue	

A cross-reference table showing how these requirements are to be met is included in Appendix A of this Quality Plan.

2.4.3 Non-Conformances with User Requirements

TBA: Explanatory note (delete this before publication):
List out any non-conformances
The following non-conformances exist between this document and the User Requirement Specification:

Requirement Reference	Requirement	Comment

2.4.4 Relationship to Supplier's Quality System

TBA: Explanatory note (delete this before publication): include detail on the formal quality management systems in use

Example for applications engineered by Eurotherm in the UK (group companies with their own ISO certification will be similar):
The Quality Management System of Eurotherm Limited has been approved by Lloyd's Register Quality Assurance to ISO9001:2000 and the TickIT guide Issue 5.

Example for applications engineered in Eurotherm Group companies without their own ISO certification who act as satellite offices and use UK procedures):
All Eurotherm Limited products used on this project have been developed and manufactured under a Quality Management System approved by Lloyd's Register Quality Assurance to ISO9001:2000 and the TickIT guide Issue 5.
All project activities are controlled according to this Quality Plan including the use of the same Systems Engineering Procedures approved in the UK to ISO9001:2000 and the TickIT guide Issue 5.

3. OVERVIEW

3.1 Project Background

3.1.1 Process to be Controlled

TBA: Explanatory note (delete this before publication):
Describe the business process as understood from the customer's URS

3.1.2 Key Benefits

TBA: Explanatory note (delete this before publication):
Describe the key objectives / benefits as understood from the customer's URS

3.1.3 Relevant GxP Regulations

TBA: Explanatory note (delete this before publication):
Describe the relevant GxP regulations as understood from the customer's URS
Summarise whether 21CFR part 11 applies and if so to which records and/or signatures

3.1.4 Impact on Patient Safety, Product Quality and Data Integrity

This system has been classified by the end user as:
TBA: Explanatory note (delete this before publication): -
The customer should already have done the first step of the risk assessment and the GxP criticality / impact level of the system should be available either in the URS or a separate risk assessment document.
Update this table as relevant to the project and if necessary add some words about what the customer means by high/medium/low.

GxP Critical	Yes / No
Impact Level	High / Medium / Low

3.2 Project Boundaries and Interfaces

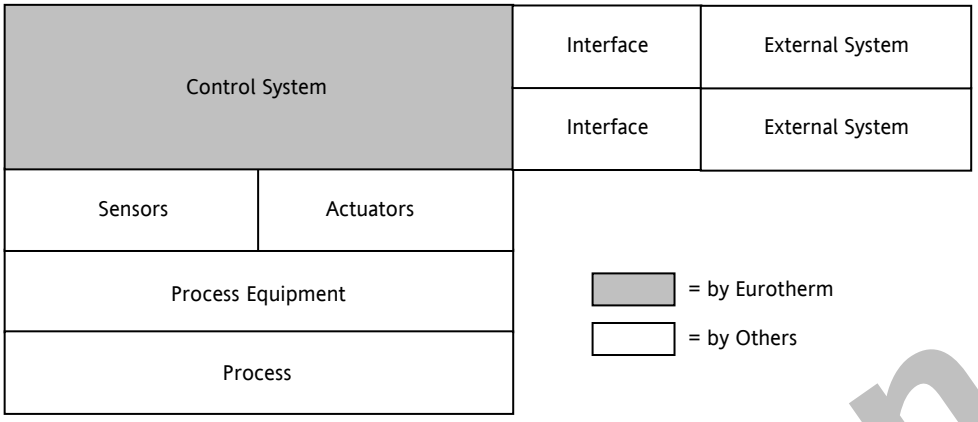
TBA: Explanatory note (delete this before publication):
Modify the drawing to show the correct boundary for the scope of supply / validation
– remove right hand boxes from each if no external interfaces are involved, specify what equipment (eg 'Siemens PLC') and what type of interface (eg 'Modbus interface') if they are involved.

The example (here and for the remainder of the document) assumes typical Eurotherm scope when supplying a stand alone control system.

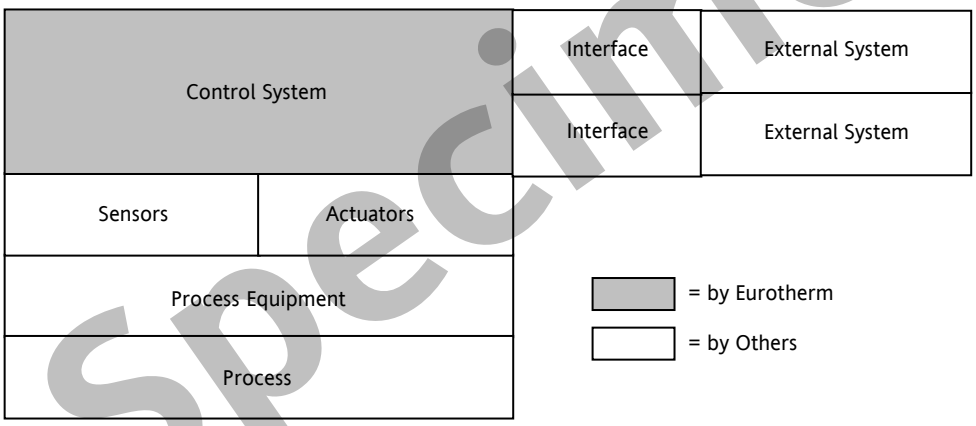
- *If sensors are also part of the validation scope then associated activities will need to be added into all sections (eg loop calibration, verification of any certification (eg certificates of conformity, ATEX ratings), control of any configurations from smart transmitters, etc)*
- *If actuators are also part of the validation scope then associated activities will need to be added into all sections (eg verification of any certification (eg certificates of conformity, ATEX ratings), control of any configurations, etc)*
- *WARNING: If process equipment is also part of the validation scope then specialist assistance will be required and associated activities will need to be added into all sections (eg verification of product contact materials, surface finish, cleaning validation, verification of appropriate certification (eg welding, pressure testing), etc)*
- *WARNING: If process is also part of the validation scope then specialist assistance will be required and associated activities will need to be added into all sections (eg validation to demonstrate capability of process against original design space)*

Project Boundaries are as follows:

Scope of Supply



Scope of Validation

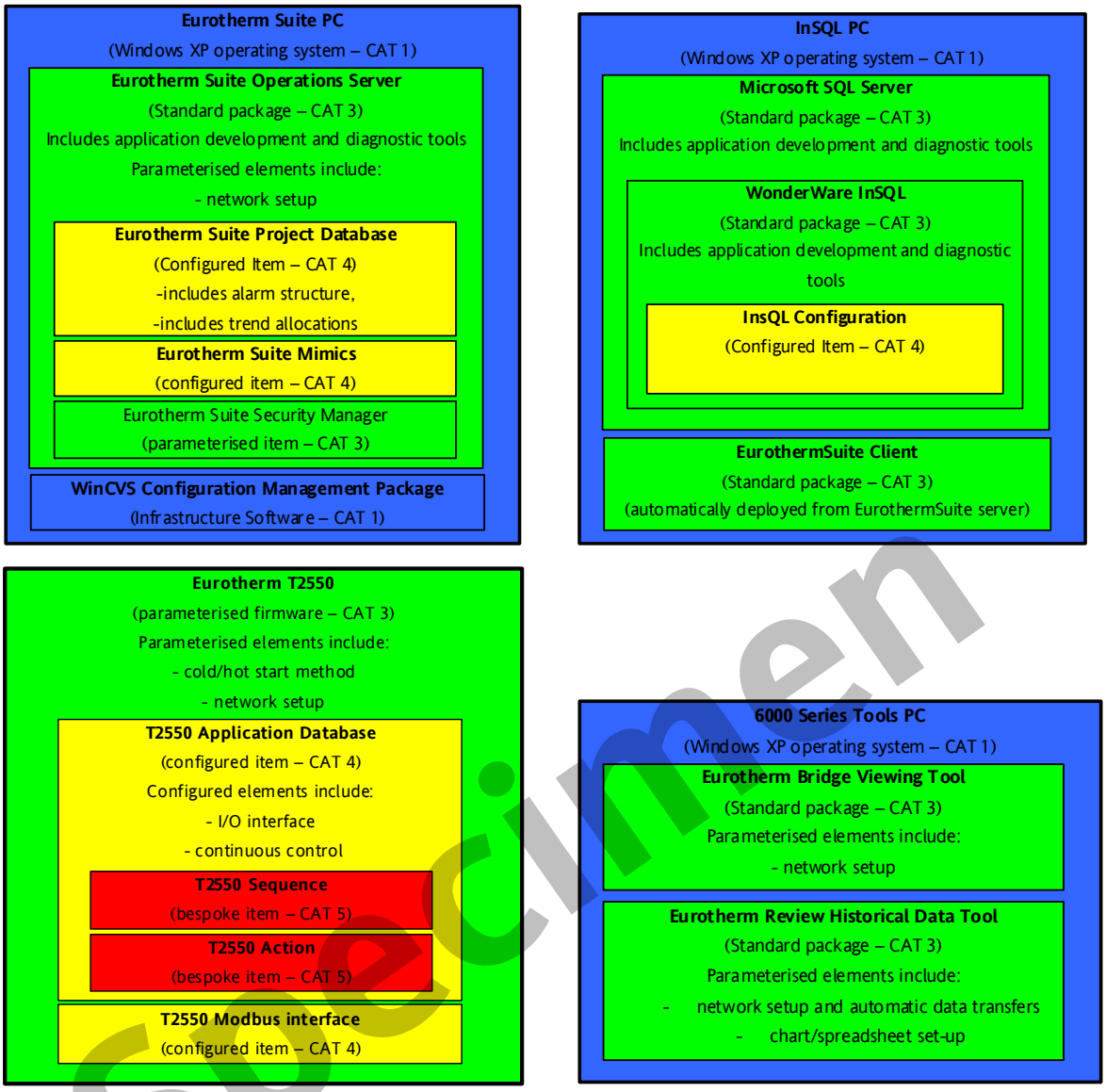


3.3 System Overview – Hardware Architecture

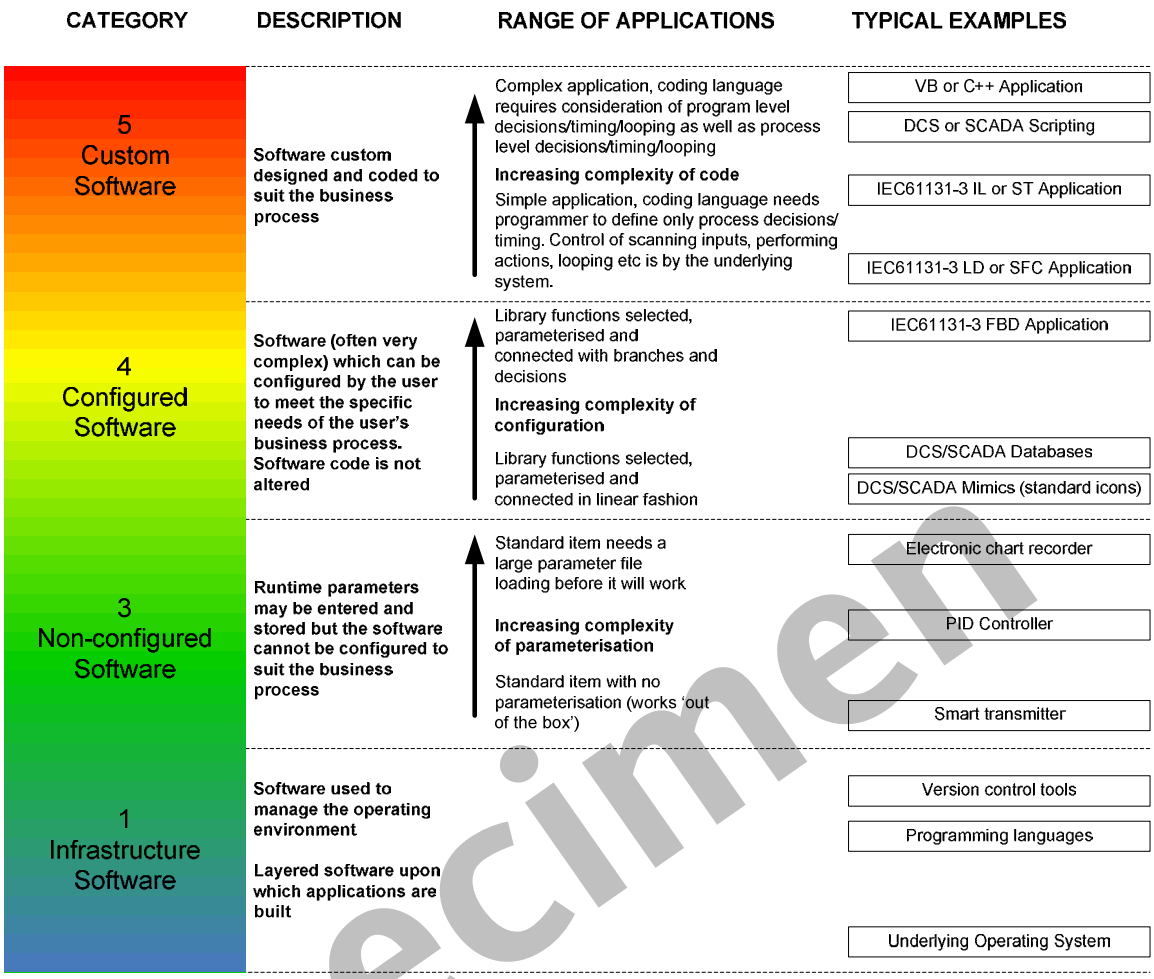
The following diagram provides an overview of the control system hardware.
TBA: Explanatory note (delete this before publication): - hardware architecture summary (diagram is probably available from quote, if not then create one)
TBA: Explanatory note (delete this before publication): state whether there is any hardware which is not classified as GAMP5 category 1 (standard hardware)

3.4 System Overview – Software Architecture

The following diagram provides an overview of the control system software giving GAMP5 classifications:
TBA: Explanatory note (delete this before publication): software architecture summary should show categorisation of the various elements – do not necessarily need to know exact detail on sequences, actions etc at this stage; just include an example. The following diagram can be used as a starting point:

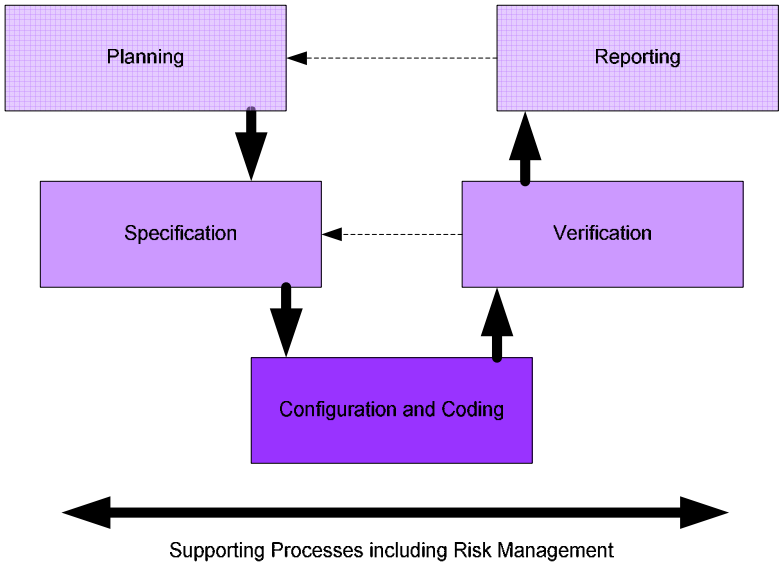

Eurotherm Suite PC
(Windows XP operating system – CAT 1)
Eurotherm Suite Operations Server
(Standard package – CAT 3)
Includes application development and diagnostic tools
Parameterised elements include:
- network setup
Eurotherm Suite Project Database
(Configured Item – CAT 4)
-includes alarm structure,
-includes trend allocations
Eurotherm Suite Mimics
(configured item – CAT 4)
Eurotherm Suite Security Manager
(parameterised item – CAT 3)
WinCVS Configuration Management Package
(Infrastructure Software – CAT 1)
InSQL PC
(Windows XP operating system – CAT 1)
Microsoft SQL Server
(Standard package – CAT 3)
Includes application development and diagnostic tools
WonderWare InSQL
(Standard package – CAT 3)
Includes application development and diagnostic tools
InsQL Configuration
(Configured Item – CAT 4)
EurothermSuite Client
(Standard package – CAT 3)
(automatically deployed from EurothermSuite server)
Eurotherm T2550
(parameterised firmware – CAT 3)
Parameterised elements include:
- cold/hot start method
- network setup
T2550 Application Database
(configured item – CAT 4)
Configured elements include:
- I/O interface
- continuous control
T2550 Sequence
(bespoke item – CAT 5)
T2550 Action
(bespoke item – CAT 5)
T2550 Modbus interface
(configured item – CAT 4)
6000 Series Tools PC
(Windows XP operating system – CAT 1)
Eurotherm Bridge Viewing Tool
(Standard package – CAT 3)
Parameterised elements include:
- network setup
Eurotherm Review Historical Data Tool
(Standard package – CAT 3)
Parameterised elements include:
- network setup and automatic data transfers
- chart/spreadsheet set-up

GAMP5 software categorisation in the above diagram is as follows:



3.5 Project Lifecycle Overview

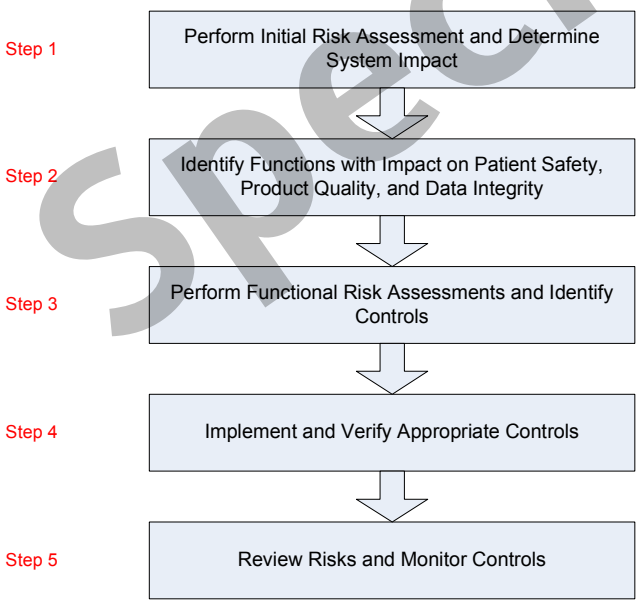
The Project lifecycle can be summarised as follows:



Specific activity requirements for this project are set out in section 4 below.

3.6 Risk Management Overview

Risk management follows the 5 step process as detailed in GAMP5:



3.6.1 Step 1 – Initial Risk Assessment & Determination of System Impact

This step has already been performed by the end user resulting in the system classification as detailed above in section 3.1.4.

3.6.2 Step 2 – Identify Functions with Impact on Patient Safety/Product Quality/Data Integrity

The impact on patient safety, product quality and data integrity of each functional and data requirement for the system is detailed by the end user in the following document:

TBA: Explanatory note (delete this before publication): - update this table as relevant to the project

Some customers will provide categorisation of requirements within their URS. Others will supply a separate risk assessment document. If a customer has no suitable risk assessment procedures in place, Eurotherm has a risk assessment template which can be used but the activity should remain the responsibility of the end user as Eurotherm can have no way of knowing the impact on patient safety/product quality of the various requirements .

Project / Document Ref	
Title	
Issue	

3.6.3 Step 3 – Perform Functional Risk Assessment and Identify Controls

On completion of the functional specification, those functions previously identified as having impact on patient safety, product quality and data integrity will undergo risk assessment (jointly by Eurotherm and the end user) as follows:

LOW impact functions	No further assessment required – scale lifecycle activities as detailed in the table under step 4
MEDIUM impact functions	Risk assessment considers generic hazards with functions assessed against a generic list of scenarios/controls. Combining scores for severity, likelihood and probability of detection results in a risk priority for each function which is used to decide upon appropriate controls.
HIGH impact functions	Risk assessment considers specific hazards. Combining scores for severity, likelihood and probability of detection results in a risk priority for each function which is used to decide upon appropriate controls.

3.6.4 Step 4 – Implement and Verify Appropriate Controls

The output of the risk assessment process is used to decide upon appropriate controls. A range of options is available to provide the required control depending on the identified risk. These include, but are not limited to:

- Modification of process design or system design
- Application of external procedures
- Increasing the detail or formality of specifications
- Increasing the number and level of detail of design reviews
- Increasing the extent or rigor of verification activities

For purposes of validation planning, each software or hardware element inherits the highest risk priority of any function it performs. The risk priority is then used to decide on appropriate scaling of validation activities as detailed in the following table:

<table>
<tr><th>Lifecycle Phase / Supporting Activity</th><th>Infrastructure software element</th><th>Non-configured software element</th><th>Configured software element</th><th>Bespoke software element</th></tr>
<tr><td>Planning</td><td colspan="4">Quality plan</td></tr>
<tr><td rowspan="5">Specification</td><td colspan="4">Functional Specification (may also detail design and configuration on a simple / low risk system)</td></tr>
<tr><td colspan="2"></td><td colspan="2">Hardware Design and Configuration Specification if justified by HIGH/MEDIUM risk priority or by the complexity of the hardware</td></tr>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Software Design and Configuration Specification if justified by HIGH/MEDIUM risk priority or by the complexity of the software</td></tr>
<tr><td></td><td>Software Module Specification if justified by HIGH/MEDIUM risk priority or by the complexity of the software</td></tr>
<tr><td colspan="4">For all categories of software, settings and parameters which are critical to meeting user requirements are detailed within the documentation. All other settings and parameters are controlled electronically via baselines of the software taken prior to each verification phase and at project handover. The ‘as handed over’ settings and parameters are supplied to the end user within the software baseline on CD/DVD. Subsequent modifications made on-line are controlled via the audit trail. Subsequent modifications made off-line are controlled via the configuration management system and result in a new baseline being taken.</td></tr>
<tr><td>Configuration and coding</td><td colspan="2">Parameter entry</td><td>Configuration</td><td>Coding</td></tr>
<tr><td rowspan="5">Configuration Management</td><td colspan="2">Parameter file saved to project repository.</td><td>Configuration file saved to project repository.</td><td>Software source file saved to project repository.</td></tr>
<tr><td colspan="2">Control (baselining) starts prior to first formal test activity involving the item.</td><td>Control (baselining) starts prior to first formal test activity involving the item</td><td>Control (baselining) starts prior to code review.</td></tr>
<tr><td colspan="2"></td><td>Where permitted by editing tools and where justified by risk/complexity, files contain text header which identifies version and change history.</td><td>Files contain text header which identifies version and change history.</td></tr>
<tr><td colspan="3">Blocks of parameter or configuration files may be controlled together as a single item where they combine to provide an identifiable function (eg operator interface screens).</td><td>Bespoke items are separately controlled; if necessary exporting them from within a configured item (eg exporting scripts from within a display) to allow separate control.</td></tr>
<tr><td colspan="4">Where settings or parameters cannot be saved to a file (e.g. dip switches used to set up a communications address or initialisation parameters which would need to be entered via the front panel if an instrument was replaced), the required settings are detailed in the Configuration Environment Schedule</td></tr>
</table>

<table>
<tr><th>Phase</th><th>Infrastructure software element</th><th>Non-configured software element</th><th>Configured software element</th><th>Bespoke software element</th></tr>
<tr><td rowspan="5">Verification</td><td rowspan="4">Assume infrastructure elements are adequately challenged by functional testing of the application</td><td></td><td></td><td>Code review</td></tr>
<tr><td></td><td></td><td>Structural (module) testing if justified by HIGH/MEDIUM risk priority or by the complexity of the software</td></tr>
<tr><td></td><td colspan="2">Factory acceptance (functional) testing including challenge testing for HIGH risk functionality</td></tr>
<tr><td colspan="3">Factory acceptance (functional) testing against user requirements</td></tr>
<tr><td colspan="4">Site acceptance test – phase 1 (installation checks)</td></tr>
<tr><td colspan="4">Site acceptance test – phase 2 (operational checks – covers those functions which may be affected by the change from factory test environment to final environment plus any functions which could not be adequately tested in the factory test environment)</td></tr>
<tr><td>Reporting</td><td colspan="4">Final Quality Report and Handover Checklist</td></tr>
</table>

Specific activity requirements for this project are set out in section 4 below.

3.6.5 Step 4 – Review Risks and Verify Controls

Once controls have been identified and implemented, the risk assessment is re-visited (again, jointly by Eurotherm and the end user) in order to confirm that risk levels have been appropriately reduced.

4. QUALITY PLANNING - PROJECT LIFECYCLE PHASES

TBA: Explanatory note (delete this before publication): This section allows the controlling procedure for each activity to be agreed (is it Eurotherm's, the customers or an external guideline / procedure such as GAMP?) ***MAKE SURE IT MATCHES THE PURCHASED LIST OF ACTIVITIES FOR THE PROJECTAND THAT THE SPLIT OF ACTIVITIES BETWEEN EUROTHERM AND THE CUSTOMER IS AS PER THE CUSTOMER'S ORDER***
Note that the references in the left hand columns are to allow activities on the project Gantt to be cross-referenced to this document – if not all activities are required then re-number to make consecutive again, if an activity (eg produce software) splits into lots of tasks on the Gantt then give each Gantt task a sub-number (eg C2.2.1, C2.2.2…). Any unplanned tasks or variations as the project progresses can also be added to the Gantt as new sub numbers of existing tasks – assuming they are covered by the relevant procedures listed here.
Note local controlling procedures should be substituted by Group companies if the UK SEP's are not in use.

The following sections define the responsibility and controlling procedures for activities within each phase of the project.

Responsibilities are coded as follows in each table:

PM	= project manager	QM	= quality manager	LE	= Lead Engineer
PE	= project engineer	SE	= service engineer	DO	= drawing office
R	= Independent Reviewer (at least senior engineer status and not the author of the item under review)				

4.1 Planning Phase

TBA: Explanatory note (delete this before publication): -
1) Since GAMP5 makes it clear that risk assessment is an activity belonging to the end user, the activity list below assumes that the customer has suitable risk assessment procedures in place. If they do not, Eurotherm has a risk assessment template which can be used but the activity should remain the responsibility of the end user as Eurotherm can have no way of knowing the impact on patient safety/product quality of the various requirements .

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
A1	Review customers URS and initial risk assessment	PM	Eurotherm SEP109	(appropriate inclusion of requirements / risk assessment is reviewed within each documentation deliverable)
A2	Generate Project Plan (Gantt)	PM	Eurotherm SEP102	Project Gantt submitted to repository
A3.1	Generate Quality Plan	PM	Eurotherm SEP109 (meets GAMP5 App M6)	Approved Quality Plan
A3.2	Review Quality Plan	QM	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
A3.3	Approve Quality Plan	(customer)	(customer)	Approved Quality Plan

4.2 Specification Phase

TBA: Explanatory note (delete this before publication): -
1) For smaller / simpler jobs it may be acceptable to include hardware and software design within the functional specification. In this case a single acceptance test specification usually covers hardware and software and a single witnessed factory test is held.
2) Module specifications, module test specifications, code review and module test are not generally required unless there are category 5 elements (though occasionally a category 4 item may be deemed critical enough to demand them).
3) The traceability matrix is, as a minimum, contained within each document (eg FS cross-referenced to URS, TS cross-referenced to FS…) If this is acceptable to the customer and an overall matrix has not been purchased then delete the activities relating to overall traceability matrix (B6, D9).
4) Since GAMP5 makes it clear that risk assessment is an activity belonging to the end user, the activity list below assumes that the customer has suitable risk assessment procedures in place. If they do not, Eurotherm has a risk assessment template which can be used but the activity should remain the responsibility of the end user as Eurotherm can have no way of knowing the impact on patient safety/product quality of the various requirements .

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
B1.1	Generate Functional Specification (FS)	PM, LE	Eurotherm SEP109 (meets GAMP5 App D2)	Approved FS
B1.2	Review FS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
B1.3	Approve FS	(customer)	(customer)	Approved FS
B2.1	Generate Hardware Design and Configuration Specification (HDS) including drawing package for any custom hardware	PM, LE, DO	Eurotherm SEP109 (meets GAMP5 App D3)	Approved HDS
B2.2	Review HDS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
B2.3	Approve HDS	(customer)	(customer)	Approved HDS
B3.1	Generate Software Design and Configuration Specification (SDS)	PM, LE	Eurotherm SEP109 (meets GAMP5 App D3)	Approved SDS
B3.2	Review SDS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
B3.3	Approve SDS	(customer)	(customer)	Approved SDS
B4.1	Generate Software Module Specifications (SMS) for bespoke items	PM, LE	Eurotherm SEP109 (meets GAMP5 App D3)	Approved SMS
B4.2	Review SMS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
B4.3	Approve SMS	(customer)	(customer)	Approved SMS
B5	Assist customer with functional risk assessment	PM/LE	(customer)	(customer risk assessment documentation)
B6.1	Generation of overall traceability matrix (TM) - Phase 1 (Design coverage)	PM	Eurotherm SEP109 (meets GAMP5 App M5)	Approved TM
B6.2	Review TM	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
B6.3	Approve TM	(customer)	(customer)	Approved TM

4.3 Configuration and Coding Phase

TBA: Explanatory note (delete this before publication): If replacing a system, additional data migration activities may need to be added. The controlling procedure may be a standard upgrade path (eg from one version of Review to another) or it might involve writing a separate procedure either as an extra section of the quality plan or as a separate document – if a separate document, make sure it is added to 4.3 and 5.4.2.

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
C1.1	Order Hardware	PM/LE	Eurotherm SEP104, local purchasing.	Signed Equipment Schedule
C1.2	Build Eurotherm Product	Eurotherm Production	Eurotherm Production Procedures	(none - signed off in verification activities)
C1.3	Receive bought-in product	LE	Eurotherm SEP104, local goods inward procedures.	(none - signed off in verification activities)
C1.4	Build Bespoke hardware (e.g. cubicles)	LE + sub contract supplier	Eurotherm SEP104	Check-sheet from SEP104 completed by supplier.
C2.1	Produce configuration management schedules	LE/PE	Approved quality plan	Schedules completed
C2.2	Produce Software	LE/PE	Eurotherm SEP105/SEP106 (meets GAMP5 App D5)	(none - signed off in verification activities)

4.4 Verification Phase

TBA: Explanatory note (delete this before publication): Site testing and how it fits with IQ/OQ needs to be sorted out during the bid process. The approach given here seems to be most common: Eurotherm site acceptance phases 1 and 2 form part of the customer IQ and OQ respectively (most customers have pre-set IQ/OQ protocols which can reference a Eurotherm test alongside other 'non-Eurotherm' activities such as their own in-house calibrations, checking of SOP's, correct archiving of the project documentation, etc)

TBA: Explanatory note (delete this before publication): for projects which involve enclosures, the panel builder will have to conduct some tests (such as earthing, etc.) as listed in SEP107 and supply test results which can be referred to during FAT and/or SAT.

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
D1	Code Review (standard Eurotherm review proforma)	R	Eurotherm SEP106 (meets GAMP5 App D4)	Signed Review Report
D2.1	Generate Software Module Test Specifications (SMTS) for bespoke items	PM, LE	Eurotherm SEP109 (meets GAMP5 App D5)	Approved SMTS
D2.2	Review SMTS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
D2.3	Approve SMTS	(customer)	(customer)	Approved SMTS
D2.4	Execute Software Module Test against SMTS	PM/LE	Approved Test Specification	Signed test records
D2.5	Review Software Module Test Results	R	Approved Test Specification	Reviewed test records
D3	System Integration	PE	Manufacturer's instructions and manuals	(none - signed off in FAT phase 1)

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
D4.1	Generate Factory Acceptance Test Specification (FATS) - Phase 1 (hardware tests) - Phase 2 (functional tests)	PM, LE	Eurotherm SEP109 (meets GAMP5 App D5)	Approved FATS
D4.2	Review FATS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
D4.3	Approve FATS	(customer)	(customer)	Approved FATS
D4.4	Integrated Test (Internal) against FATS	PM/LE	Approved Test Specification	Signed test records
D4.5	Review Integrated Test Results	R	Approved Test Specification	Reviewed test records
D4.6	Factory Acceptance Test against FATS - Phase 1 (installation tests) - Phase 2 (functional tests)	PM, LE, customer witness	Approved Test Specification	Signed test records
D4.7	Review Factory Acceptance Test Results	Customer reviewer	Approved Test Specification	Reviewed test records
D5	Ship to site	LE	Eurotherm SEP104	Signed Shipment Request
D6	Installation	(customer)	Manufacturer's instructions and manuals	(none - signed off in SAT phase 1)
D7.1	Generate Site Acceptance Test Specification (SATS) - Phase 1 (installation tests) - Phase 2 (functional tests)	PM, LE	Eurotherm SEP109 (meets GAMP5 App D5)	Approved SATS
D7.2	Review SATS	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
D7.3	Approve SATS	(customer)	(customer)	Approved SATS
D7.4	Site Acceptance Test against SATS - Phase 1 (installation tests) - Phase 2 (functional tests)	SE + customer witness	Approved Test Specification	Signed test records
D7.5	Review Site Acceptance Test Results	Customer reviewer	Approved Test Specification	Reviewed test records
D8	Loop Calibration	(customer)	(customer)	(calibration certificates)
D9.1	Generation of overall traceability matrix (TM) - Phase 2 (Test coverage)	PM	Eurotherm SEP109 (meets GAMP5 App M5)	Approved TM
D9.2	Review TM	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
D9.3	Approve TM	(customer)	(customer)	Approved TM

4.5 Reporting Phase

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document

Ref	Activity	Responsibility	Controlling Procedure	Verifying Document
E1.1	Generate system final documentation - 'as built' design documents - technical manual containing bill of materials, 'as built' configuration management schedules	PM, LE	Eurotherm SEP109	Approved 'as built' documentation
E1.2	Review 'as built' documentation	R	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
E1.3	Approve 'as built' documentation	(customer)	(customer)	Approved 'as built' documentation
E2	Provide training	Eurotherm training officer	As defined in customer order	Training certificates issued
E3.1	Generate final quality report and handover checklist	PM	Eurotherm SEP109 (meets GAMP5 App M7)	Approved final quality report handover checklist
E3.2	Review final quality report handover checklist	QM	Eurotherm SEP109 (meets GAMP5 App M9)	Signed Review Sheets
E3.3	Approve final quality report handover checklist	(customer)	(customer)	Approved final quality report handover checklist
E4	Assist customer with review of residual risks	PM/LE	(customer)	(customer risk assessment documentation)
E5	Archive documentation and configurations	LE	Eurotherm SEP108	Signed Project Closure Checksheet

4.6 Ongoing Operation Phase

TBA: Explanatory note (delete this before publication)
Include detail on any of the following which form part of the user requirements:

Any maintenance contract purchased as part of the project
Warranty period
Obsolescence policy

An example follows:

Eurotherm Limited can offer a variety of maintenance, support, parts management and call-out agreements. A support contract is not included in the scope of supply for this project and is to be negotiated separately.

All equipment shipped under the contract is subject to a parts and workmanship warranty for a minimum of 12 months from the date of shipment. The Eurotherm warranty conditions are available on request.
Upgrades are only supplied if they are mandatory or are required to remedy faults found under the warranty.

Eurotherm obsolescence policy is available on request or from the Eurotherm internet site

5. QUALITY PLANNING - SUPPORTING ACTIVITIES

5.1 Design review and traceability

Design review and traceability is in accordance with GAMP5 Appendix M5.

5.1.1 Design Review

As each design document is issued it is reviewed internally by an appropriate Eurotherm reviewer (subject matter expert) prior to issue for customer approval. The appropriate internal reviewer(s) for each document are defined in the tables in section 4 above.
All design documents are then issued for independent review and approval by the customer.

5.1.2 Traceability

Traceability is achieved through cross-reference tables in the appendix of each document.

Each design document contains a table cross-referencing its own contents to those of the controlling specification at the next highest level. For example, the functional specification would contain tables cross referencing to and from the URS.

Each test protocol contains a table cross-referencing its own contents to those of the controlling specification. For example, the factory acceptance test specification would contain tables cross referencing to and from the functional specification.

TBA: Explanatory note (delete this before publication): If customer is buying an overall traceability matrix then include the following paragraph – otherwise delete it!
In addition, an overall traceability matrix is produced in two phases:

1) Design coverage (demonstrates coverage of all user requirements within quality plan and design documents)
2) Test coverage (demonstrates coverage of all functional user requirements within test documents)

5.2 Project change management

5.2.1 Method for Controlling Changes

Change control is in accordance with GAMP5 Appendix M8. The method for controlling changes depends on the stage at which the change is required (before / after configuration is placed under control) and on whether the change is major (involves contract variation) or minor:

	Before control of documents / configurations	After control of documents / configurations
Minor change with no impact on cost or schedule	Design specification(s) re-issued with source of change listed in document records. Any test specifications affected are also re-issued. Configuration (as yet uncontrolled) is updated to match. No contract variation required	Change is indexed and documented on a change report and this is the controlling document to ensure change is made in all necessary files and documents and agree any retest requirements. No contract variation required
Major change with impact on cost or schedule	Design specification(s) re-issued with source of change listed in document records. Any test specifications affected are also re-issued. Configuration (as yet uncontrolled) is updated to match. Contract variation must be agreed before change can proceed	Change is indexed and documented on a change report and this is the controlling document to ensure change is made in all necessary files and documents and agree any retest requirements. Contract variation must be agreed before change can proceed

A sample change report is shown below.

5.2.2 Example change report

CHANGE REPORT

invensys EUROTHERM

Project *Eg Pxxxxx*	**Change Report Number** **(page of)**	**Source of change:** *Eg customer correspondence references*

Change Description

(details of the required change)

Raised By: ..... **Date:** ..... / ..... / .....

CHANGE REVIEW

Modification Agreed *(details of the modification agreed – or detail of why the change was rejected)*	**Modification and retest requirements reviewed and authorised:** *(customer representative)* **Date:**

Details of Items Requiring Modification		**IMPLEMENTATION**	
Software Affected *(list of affected software items)*	Original version	Modified version	**Implemented By:** *(usually Eurotherm engineer)* **Date:**
Documents Affected *(list of affected documents)*			**Implemented By:** *(usually Eurotherm engineer)* **Date:**
Hardware Affected *(list of affected hardware items)*			**Implemented By:** *(usually Eurotherm engineer)* **Date:**

Retest Requirements *(list of required retests if changes affect items which have already been tested – eg Re-run FAT-001A steps 1-5)*	**RETEST** **Test Passed By:** *(usually Eurotherm engineer)* **Date:**

CLOSURE following changes and successful re-test or agreement to abort test
(usually Eurotherm project manager if change made before start of witnessed testing, customer representative thereafter)
Fault Closed By: ..... **Date:** ..... / ..... / .....

5.3 Project configuration management

TBA: Explanatory note (delete this before publication): - some customers ask for a separate configuration management plan. If so, this section can be taken out into a separate document with an introduction section (purpose, scope, contractual status, relationship to other documents) similar to that for the Quality Plan. Don't forget to include the extra document in the documentation deliverables above.

Configuration management is in accordance with GAMP5 Appendix M8 / O6.

5.3.1 Configuration Identification

TBA: Explanatory note (delete this before publication): - this section defines WHAT we are going to control. For a very small system it may be possible to list software items here but it is normally easiest to keep a separate schedule which can be updated without the need to up-issue the quality plan.

Project software is categorised in line with the guidance in GAMP5 Appendix M4 as detailed in section 3.4 above.

Configuration Environment

A Configuration Environment Schedule consisting of a list of infrastructure and non-configured software items is issued separately for ease of update. All category 1 and 3 items are listed along with installed version numbers.

Where parameters cannot be saved to a file (e.g. dip switches used to set up a communications address or initialisation parameters which would need to be entered via the front panel if an instrument was replaced), the required settings are detailed in the Configuration Environment Schedule.

Configuration Items to be Controlled

A Configuration Management Schedule consisting of a list of software items to be controlled is issued separately for ease of update. All category 4 and 5 items are listed along with parameter files for any category 1 or 3 items where appropriate.

Blocks of parameter or configuration files may be controlled together as a single item where they combine to provide an identifiable function (eg operator interface screens). Bespoke items are always separately controlled; if necessary exporting them from within a configured item (eg exporting scripts from within a display) to allow separate control.

5.3.2 Configuration Control

TBA: Explanatory note (delete this before publication): - this section defines HOW we are going to control it.

- How is the version identified within the configuration management system?

- Can the version be identified from within the application development tool? – eg by a text header – this will definitely be required for bespoke coded items but may not be possible for many configured items such as Wonderware mimics for example.

- Can the version in use be identified from within the runtime environment? – for example EYCON and T2550 show checksums when viewed via Eurotherm network explorer the in use version can be positively confirmed, 6000 series instruments maintain an automatic version number which is automatically incremented on each save.

Example below assumes use of a WinCVS repository as on projects in the UK.

Configuration management is via **WinCVS (Concurrent Versions System)**; a widely used version control tool for tracking all modifications to project source code files

Version Control

Each configuration item to be controlled is placed into a project repository. Formal control commences at the following stages:

Item Type	Stage For Control
Parameter files for Category 1, 3 items	Before first formal test activity involving the item (normally integrated test)
Configurations for Category 4 items	Before first formal test activity involving the item (normally integrated test)
Code for Category 5 items	Before code review

Formal configuration control is applied via baselines taken at critical stages of the project. A baseline is created using the 'tagging' facility within WinCVS to label all files involved in a particular activity (eg a tag 'ForCodeReview_ModuleX' might be applied to all files involved in ModuleX before code review commences; a tag 'ForFAT' might be applied across all files prior to start of factory acceptance test)

Baselines of the configuration items will be taken at the following critical project milestones (as a minimum).
TBA: Explanatory note (delete this before publication): - update this table as relevant to the project. Example below can be reduced if no cat5 software or if the customer takes control of configurations as soon as they reach site – the minimum on any job should be each formal test stage plus AsHandover.

Milestone	Tag
Prior to code review	ForCodeReview_(module name)
Prior to module test	ForModTest_(module name)
Prior to in-house system acceptance test	ForIntTest
Prior to witnessed system acceptance test at suppliers factory	ForFAT
As accepted / shipped	AsShipped
Prior to witnessed system acceptance test at customer site	ForSAT
As final acceptance / handover to site	AsHandover

Version identification from within the application development tools:
Source files for bespoke software items (all category 5 items) and configurations (where editing tools permit and where justified by risk/complexity) will have a text header containing the following information:

- Module name
- Details of other source or compilation files (eg map files for generic sequences)
- Project name and number
- Brief description of the module
- Change history including version number, date, person making change, details of change (including reference to fault/change report)

Where a editing tools do not allow text header information (various category 3 and 4 items e.g. mimic definitions), the version will be taken entirely from the project repository within the configuration management tool.

Version identification from within the runtime environment:
On this system the following runtime version information will be available:
TBA: Explanatory note (delete this before publication): - update this table as relevant to the project

6000 Series Recorder	Automatically generated configuration and security versions are visible

	from the 'about' menu.
EYCON Visual Supervisor	Checksum visible in Eurotherm Network
T2550 Unit Supervisor	Checksum visible in Eurotherm Network

Version identification from within the configuration management tool:
Version information available in the runtime environment and versions recorded in file headers will be linked to the project repository by using the note which is entered a file is committed to the repository. For example, if following module test actions, a T2550 sequence file is at version 3 in its own file header and shows a checksum of ABC123 in Eurotherm Network, the note entered as it is committed to the repository would record:

File header version: 3
Checksum: ABC123
Reason for change: Module test actions 1,2,3,4 completed.

Change Control

Change control as defined in section 5.2 of the Quality and Project Plan is applied to all configuration items.

Configuration Item Storage

TBA: Explanatory note (delete this before publication): - this section needs to detail:

- *How do we protect items from unauthorised changes?*
- *How do we back up and, if necessary, recover items?*
- *Are suitable anti-virus precautions in place?*

The examples below describe the situation in the UK. Please alter as appropriate for use elsewhere if DP009 not in use.

During the development phase of the project, all configuration items are stored in the project repository in the project directory on a Eurotherm fileserver. Access control, backup, maintenance and virus protection are then to Eurotherm procedure DP009 – Information Technology Department.

On delivery to the customer, the master copy of the repository can be transferred if required or the controlled files can be transferred to the customer's configuration management system. Responsibility for configuration management and adequate backup passes to the customer.

Release Management and Delivery

TBA: Explanatory note (delete this before publication): - this section needs to detail:

- *How do we control release of files to the customer?*
- *How does the customer know what has changed since the last release?*
- *How does the customer know of any known errors, workarounds, pending change requests?*
- *How does the customer know if there is a dependency between versions or a dependency on a particular hardware or software platform?*
- *How does the customer know how to install a new version of a delivered item?*

The example below assumes use of a WinCVS repository

Handover of configuration files to the customer is controlled as follows:

- A check is carried out that all items have been returned to the master copy of the repository.
- The current configuration is tagged for release.
- A release documentation package is prepared consisting of the following:

- Up-to-date configuration environment schedule
- Up-to date configuration management schedule
- Details of baseline applied for the release
- Copy on CD or DVD of all controlled files
- Listing of any known errors / workarounds / pending change requests.

- If the master copy of the repository has been transferred to the customer, a check is made that an up-to-date copy of all controlled files has been retained at Eurotherm.

5.3.3 Configuration Status Accounting

TBA: Explanatory note (delete this before publication): - this section needs to detail:

- *How do we know what are the current versions?*
- *Can we find out the history of a particular file?*

The example assumes WinCVS is in use

Configuration status (including version, up-to-date / modified status for the working directory) and history (version numbers, change references, baselines) is maintained automatically by the WinCVS configuration management tool and can be printed at any time.

5.3.4 Configuration Evaluation

TBA: Explanatory note (delete this before publication): - this section needs to detail:

- *How to verify the control*
- *How is the above documentation controlled, reviewed, approved?*
- *For manually controlled configurations (ie no automatic status/history as in 3.3 above) this section would also need to address how you ensure the configuration status is up-to-date.*

Configuration Status is automatically generated and therefore requires no manual checking.
The Configuration Management Plan is subject to review and approval as part of this Quality Plan.
Release documentation is subject to review and approval as part of the final Quality Report and Handover Checklist.

5.4 Document management

5.4.1 Method for Controlling Documents

Documentation delivered to the customer is controlled in accordance with Eurotherm SEP109 (written to conform to GAMP5 Appendix M9).
The document history, document approval record and document controlled circulation list are embedded within the document. A master document index is updated on each issue of a document.

Documents are stored to a file server. File identification for documents is of the form ProjectRef_DocumentName_x where x is the issue number of the document. The issue is a numeric for formal issues and has an alpha character added for draft versions (e.g. version 1a is a draft which becomes version 1 following inclusion of internal review comments).

Document change tracking commences with the first formal issue at version 1. Following this, if an update to a document is needed, a new version of a document is created and issued as follows:

1. The previous version is saved with the new version identifier plus an ‘a’ in the filename (e.g. ‘2a’) so that draft status can be identified immediately from the file name.
2. The document is opened and a printed watermark saying ‘DRAFT’ is added to ensure that draft status can be identified immediately on any printed copy.
3. All previously tracked changes are accepted.
4. The version information on the front sheet is updated to the new version identifier (e.g. ‘2’) and date.
5. The required changes are made with change tracking enabled. If sections are removed, the section heading is left with a comment that it has been removed so as to maintain traceability cross-references.
6. The document history is updated detailing the changes made (including section reference and reason for change).
7. The draft document is reviewed internally (this may be done in either electronic or paper format).
8. The draft is saved with the new version identifier (e.g. ‘2’) in the filename.
9. Any changes resulting from the internal review are made with change tracking enabled.
10. The document history and issue date (front sheet and history) are updated if appropriate.
11. The reviewer confirms that the required changes have been made and signs off the review.
12. The ‘DRAFT’ watermark is removed.
13. Tracked changes are hidden and the document printed.
14. The preparer and reviewer both sign the document front sheet.
15. The master document index is updated.
16. The document is issued to each recipient on the controlled circulation list.

5.4.2 Documentation Deliverables

TBA: Explanatory note (delete this before publication): - The table below should be updated to reflect the lifecycle given in section 4. Items which are not required should be deleted. Additional items (eg if calibration or training are part of the scope) can be added. Items should be split if necessary (eg separate SDS requested for Eycon and ESuite, separate module spec for each sequence).
If the customer has not requested their own document references, the first column may be deleted.

The following table details the documentation deliverables. Documents designated 'Live' will be updated to 'as built' status as part of the final documentation package. Other documents represent a snapshot of the system at a point in time and will not be updated.

Customer Doc Ref	Deliverable Item	Live?	Identification	Format of file	Format for Approval	Format for Final Issue
	Quality Plan	No	Double-click HERE and type Eurotherm Reference_QualityPlan_x.doc	MS Word	Electronic submission	Signed paper master
	Functional Specification	Yes	Double-click HERE and type Eurotherm Reference_FunctionalSpec_x.doc	MS Word	Electronic submission	Signed paper master
	Hardware Design Specification	Yes	Double-click HERE and type Eurotherm Reference_HDS_x.doc	MS Word	Electronic submission	Signed paper master
	Drawings Package associated with hardware design	Yes	Double-click HERE and type Eurotherm Reference_DrawingNumber_Sheet_x.dwg	AutoCad	Electronic submission	Paper copy
	Software Design and Configuration Specification	Yes	Double-click HERE and type Eurotherm Reference_SDS_x.doc	MS Word	Electronic submission	Signed paper master
	Software Module Specification	Yes	Double-click HERE and type Eurotherm Reference_SMS_ModuleName_x.doc	MS Word	Electronic submission	Signed paper master
	Software Code Review Report	No	Double-click HERE and type Eurotherm Reference_CodeReview_ModuleName_x.doc	MS Word	Not required (standard pro-forma)	Signed paper master
	Software Module Test Specification	No	Double-click HERE and type Eurotherm Reference_SMTS_ModuleName_x.doc	MS Word	Electronic submission	Signed paper master
	Factory Acceptance Test Specification	No	Double-click HERE and type Eurotherm Reference_FATS_x.doc	MS Word	Electronic submission	Signed paper master
	Site Acceptance Test Specification	No	Double-click HERE and type Eurotherm Reference_SATS_ x.doc	MS Word	Electronic submission	Signed paper master
	Software Module Test results files	No	(hand written test result collated into file)	Paper master	Not required	Paper master
	FAT results files	No	(hand written test result collated into file)	Paper master	Not required	Paper master
	SAT results files	No	(hand written test result collated into file)	Paper master	Not required	Paper master

Customer Doc Ref	Deliverable Item	Live?	Identification	Format of file	Format for Approval	Format for Final Issue
	Overall Traceability Matrix	Yes	Double-click HERE and type Eurotherm Reference_TM_ x.xls	MS Excel	Electronic submission	Signed paper master
	Final Quality Report and Handover Checklist	Yes	Double-click HERE and type Eurotherm Reference_QualityReport_ x.doc	MS Word	Not required	Signed paper master
	Standard Manuals	Yes	(supplied on Eurotherm Suite CD)	Online books	N/A	Online books
	Technical Manual	Yes	(collated into Technical Manual file)	(note 1)	Not required	Paper master

TBA: Explanatory note (delete this before publication): - An example of setting out the requirements for a Technical Manual is included here. Thisshould be changed to reflect the deliverables appropriate to the project and may be added to if, for example, SOPs or loop calibration has been sold as part of the project.

Note 1 – The following contents are collated into the Technical Manual file:

Technical Manual Item
IOM Manual Index
Bill of Materials with serial numbers and software licence details
Manufacturer's Calibration Certificates
Hardware Specification Sheets
Configuration Environment Schedule
Configuration Management Schedule

5.5 Sub-contractor Control

Sub-contractors who work to their own procedures to produce a standard product are controlled through Eurotherm's local purchasing procedures.

TBA: Explanatory note (delete this before publication): - If any sub-contractors are to be used, how is quality ensured? Do they work to Eurotherm procedures or their own? Is their quality system externally accredited? What certification/ evidence will be supplied for filing as part of the project? Some possible examples are included.

The following sub-contractors are to be used to provide bespoke products or services as part of this project:

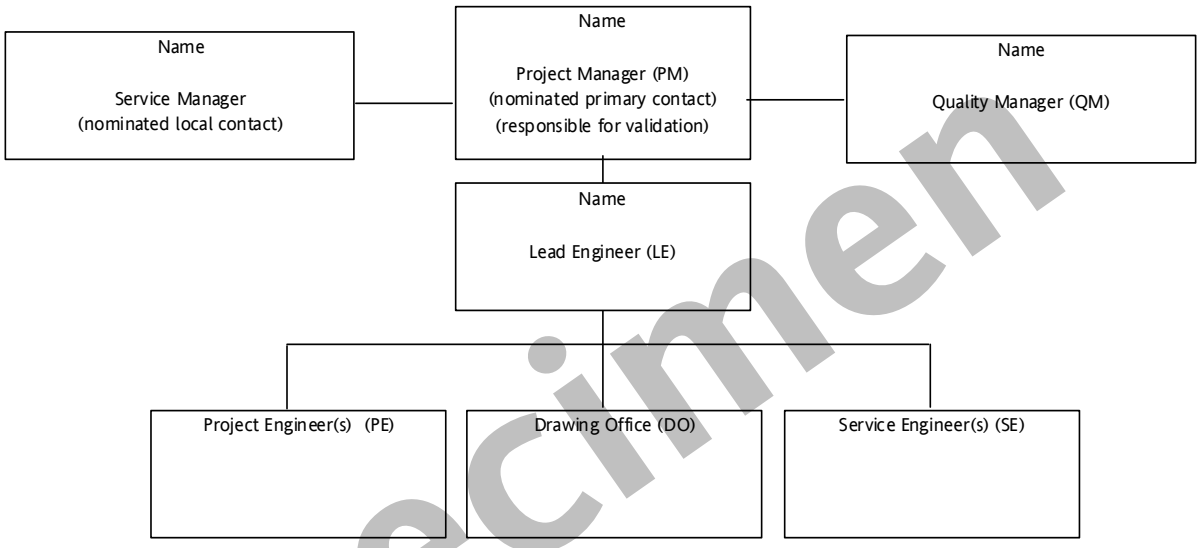
Company	Type of Supply	External Accreditation	Certification / Control requirements
(example panel builder 1)	Design and manufacture of control enclosures	ISO9001	Copy of ISO9001 certificate Copy of Eurotherm's supplier qualification sheet
(example panel builder 2)	Manufacture of control enclosures to Eurotherm design working to Eurotherm procedure SEP104	None	Copy of Eurotherm's supplier qualification sheet Copy of SEP104 check sheet filled in by panel builder
(example validation consultant)	Project Management and Validation Services	None	Copy of Eurotherm's supplier qualification sheet Copy of consultant's training / competence records

6. PROJECT PLANNING

6.1 Project Organisation

TBA: Explanatory note (delete this before publication): - Organisational chart is required giving names and job titles for responsible personnel.

- *Nominated primary contact should be shown*
- *Person with responsibility for validation should be shown*
- *Interface to quality department should be shown*
- *If people show on the project Gantt by initials rather than name, then initials should also be included for ease of cross referencing.*



TBA: Explanatory note (delete this before publication): Also note the nominated point of contact for the customer.

The nominated point of contact for Double-click HERE and type Customer Name is:

6.2 Activities

TBA: Explanatory note (delete this before publication): - The project plan needs to define milestones and activities. The start and end dates of each activity should be clear, as should the personnel allocated to the activity. A separate project Gantt chart is usually the easiest way to manage this as the quality plan does not then need re-issuing on every change to the project plan. Note that the activities should normally be cross-referenced between this document and the Gantt (eg by activity reference as given in section 4 above)

A Project plan in Gantt chart format is issued separately for ease of update. The project plan shows the following:

- Project milestones
- Project activities (as listed in section 4 above)
- Personnel allocated to activities
- Planned start and end dates for each activity

The project plan is controlled by the Eurotherm Project Manager.
The plan is version controlled, with any change in milestone dates or timescales resulting in a new version.

6.3 Progress Reporting

TBA: Explanatory note (delete this before publication): - Enter details of how/when project progress is to be reviewed and reported – the example below is from a large project where we were required to submit formal fortnightly progress reports, on smaller projects the customer is often happy just to get Gantt updates if there is a change in milestone / delivery dates:

Progress against the project plan is reviewed fortnightly and reported to the customer within a fortnightly report. The fortnightly report covers the following items:

- Progress Summary (Progress against project plan, current areas of concern)
- Project Team Status (Current team members, project team issues)
- Changes/Modifications (Variations, minor changes)
- Outstanding Issues (Actions from meetings, technical queries, other issues)

The project plan is re-issued to the customer following any change in project milestone dates or timescales.

7. GLOSSARY

TBA: Explanatory note (delete this before publication): - add any other abbreviations or project-specific terms

ATEX	The abbreviation ATEX is derived from the French term "Atmospheres Explosibles" and covers two European Union Directives: 94/9/EC and 1999/92/EC.
FAT	Factory Acceptance Test
GAMP	GAMP 5 A Risk Based Approach to Compliant GxP Computerized Systems
GxP Compliance	Meeting all applicable pharmaceutical and associated life-science regulatory requirements
IQ	Installation Qualification at customer's premises
OQ	Operational Qualification at customer's premises
PQ	Performance Qualification at customer's premises
SAT	Site Acceptance Test
SEP	Eurotherm Systems Engineering Procedure
SOP	Standard Operating Procedure
URS	User Requirements Specification

APPENDIX A – CROSS-REFERENCE TO CUSTOMER QUALITY REQUIREMENTS

TBA: Explanatory note (delete this before publication): - the following tables need to be completed in order to demonstrate that the customer's quality requirements (from URS or VP as appropriate) have been met.
Any non-compliance should be highlighted in the table
Where a section includes no relevant requirements, this should be made clear

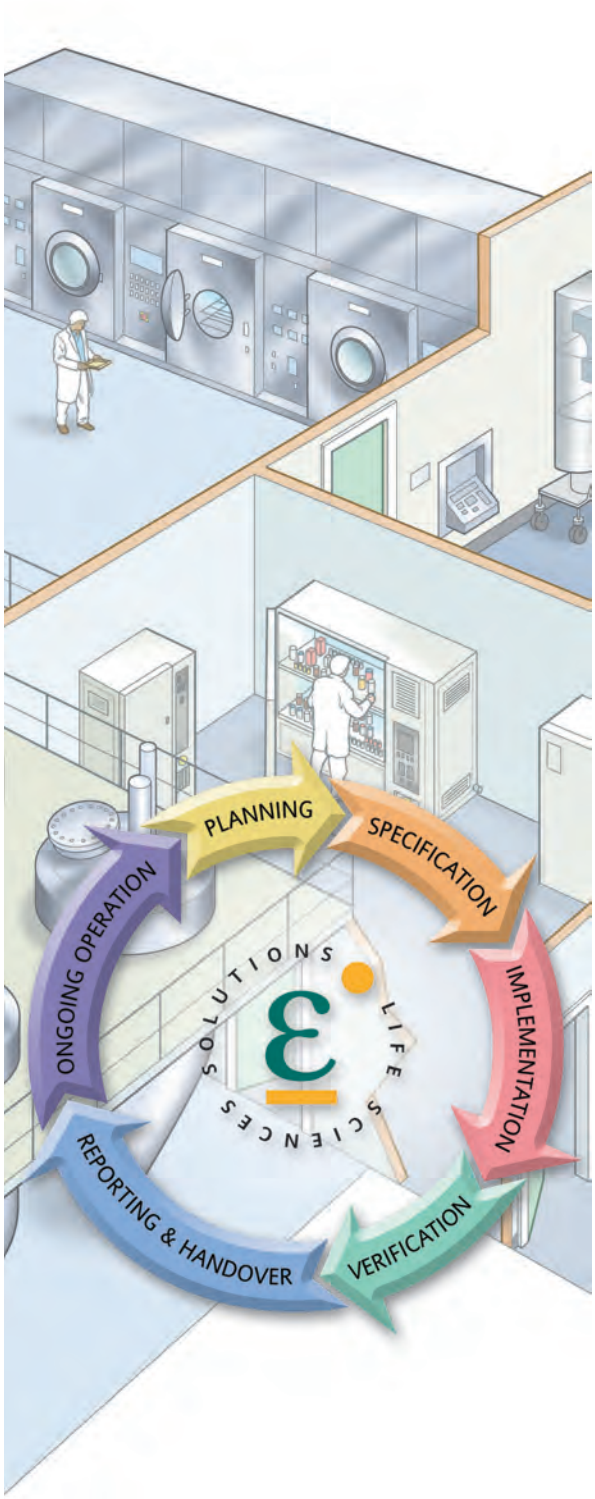
An example is shown below

(The easiest way to create these tables is via a Microsoft Access database – create separate tables for each document and then create additional tables containing just a list of links between two documents. A query can then be used to export the data in the appropriate order)

URS Ref	URS Heading	Quality Plan Ref
1.	DOCUMENTATION RECORDS	(no quality requirements listed)
2.	INTRODUCTION	(no quality requirements listed)
3.	OVERVIEW	(no quality requirements listed)
4.	FUNCTIONS	(no quality requirements listed)
5.	DATA HANDLING	(no quality requirements listed)
6.	INTERFACES	(no quality requirements listed)
7.	VALIDATION REQUIREMENTS	(no quality requirements listed)
7.1	Project Lifecycle Phases	(no quality requirements listed)
7.1.1	Planning	4.1
7.1.2	Specification	4.2
7.1.3	Configuration and Coding	4.3
7.1.4	Verification	4.4
7.1.5	Reporting	4.5
7.2	Supporting Activities	(no quality requirements listed)
7.2.1	Risk management	5.1
etc	etc	etc

QPlan Ref	Quality Plan Heading	URS or VP Ref

Life Sciences CATALOGUE



REGULATIONS 2

21CFR Part 11

- EurothermSuite® Operations Server/Viewer and 21 CFR Part 11
- Eycon™ Visual Supervisor and 21 CFR Part 11
- 6000 Series Recorders and 21 CFR Part 11

Appendix 1 and 2 include reprints from some of the applicable 21 CFR's and Guidance documents..

OpsF,OpsS, OpsW

MODELS

EurothermSuite® Operations Server/Viewer and 21 CFR Part 11

SUB PART B – ELECTRONIC RECORDS

11.10 Controls for closed systems	
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records	Eurotherm has a long history of working to formal design standards including the industry-recognised approach given in GAMP. We have many years of experience assisting our customers in achieving validation of their control systems. Our quality management and test procedures are open to your inspection and approval, with the master copy of our formal test records supplied for inclusion in your validation package.
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.	**Trended Data** – Electronic version in daily files suitable for removal / archive – Human readable version retrievable to screen / print within the system – Conversion utility to allow DDE transfer to other applications (eg Excel). **Alarm and Event History** – Covers alarms, messages, audit trail of operator actions – Electronic version in SQL database form – Human readable version retrievable to screen / print within the system – Export utility allows text version to be taken away **Reports** – Available via Report Manager software package – Electronic version in text files – Human readable via screen viewer and print

SUB PART B – ELECTRONIC RECORDS (continued)

11.10 Controls for closed systems (continued)	
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	***Current status*** Trend data and alarm and event history (including audit trail details) are read-only from normal (captive) operator interface. Trend data files for archive are in compressed (tamperproof) format. Alarm and event history, and Audit Trail are archived into tamperproof file. Reports in text format need protection via SOP Choice of archive media available (tape, CD, etc) ***Next release*** Reports in tamperproof format
(d) Limiting system access to authorized individuals.	Security system allows access to be limited both by user group (e.g. operator) and by plant area.
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	Runtime audit trail automatically records date/time, userID, action carried out to the alarm and event history tamperproof file. Separate audit trail entry is generated for each action so as not to obscure previous actions and where appropriate it will record previous value before user change.. Archival of audit trail as in (c) above.
(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.	Can be done by sequencing within Process Automation instruments or within InTouch scripting language
(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.	UserID and password entry are required in order to gain access as defined by user's status (user group) and the plant area being operated. Uniqueness of current user ID's is enforced automatically Read only user is supported
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	– I/O signals can generate alarms if invalid (eg hardware fault, out-of-range) – Operator entered data is checked for type (alpha / numeric) and range. – Format checks can be built into underlying T-series configuration – Use of software scripts can restrict mimic and data access to defined workstation
(i) Determination that persons who develop, maintain, or use electronic record/ electronic signature systems have the education, training, and experience to perform their assigned tasks.	Procedural – aided by availability of training courses from Eurotherm
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.	Procedural – assisted by the fact that standard manuals as electronic books come as part of the Eurothermsuite installation
(k) Use of appropriate controls over systems documentation including: **(1)** Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance. **(2)** Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.	 Procedural Procedural

SUB PART B – ELECTRONIC RECORDS (continued)

11.30 Controls for open systems	Not Applicable
Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in Sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality	The product is targeted at use in closed systems.

11.50 Signature Manifestations	
(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following: **(1)** The printed name of the signer; **(2)** The date and time when the signature was executed; and **(3)** The meaning (such as review, approval, responsibility, or authorship) associated with the signature.	Add printed name as well as user ID Allow pop up request for signature with associated description and, optionally, second user confirmation Store printed name, timedate, meaning when signature is executed
(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).	Identified items will be stored in alarm and event history as described in 11.10 e

11.70 Signature/Record Linking	
Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.	Store alarm/event history (containing signature details) to tamperproof file to ensure signature cannot be excised or copied by ordinary means

SUB PART C – ELECTRONIC SIGNATURES

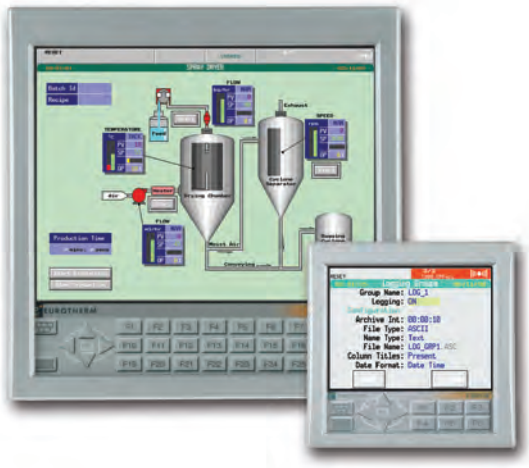
11.100 General requirements	
(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	Ensure that no two user accounts have the same username. Ensure that deleted user ID's cannot be re-created
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.	Procedural
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures. **(1)** The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations(HFC-100), 5600 Fishers Lane, Rockville, MD 20857. **(2)** Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.	Procedural

SUB PART C – ELECTRONIC SIGNATURES (continued)

11.200 Electronic signature components and control	
(a) Electronic signatures that are not based upon biometrics shall:	
(1) Employ at least two distinct identification components such as an identification code and password. **(i)** When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual. **(ii)** When an individual executes one or more signings not performed during a single,continuous period ofcontrolled system access, each signing shall be executed using all of the electronic signature components.	Requires re-entry of user ID and password during a signing. Both components will be required for all signings
(2) Be used only by their genuine owners; and	Users can change their own passwords and no read access to passwords provided;timed logout after a period of inactivity; limit number of login retries before account is disabled; minimum length for password length; password expiry after defined number of days
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	Users can change their own passwords and passwords will only appear in hidden format. Administrator functions which add users or modify the account detail of other users require authorisation by a second user
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.	Not applicable.

11.300 Controls for identification codes/passwords	
Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:	
(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	All user names are forced to be unique.
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password ageing).	Force password expiry after defined time period. If a user leaves, account can be deleted but user ID will remain within uniqueness checks
(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.	Procedural – Compromised accounts can be disabled. On loss of password, the administrator may set a new password for an account which the account holder should then immediately replace by a password of their own.
(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.	It is possible to have logins time out after a set period of inactivity; to limit the number of login retries before an account is disables; to set a minimum length for paswords; and to force password expiry after a set number of days. Failed logins that disable accounts are detailed in the Audit Trail within the system.
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.	Procedural

Eycon™ SERIES Visual Supervisor



Eycon™ Series Visual Supervisor and 21 CFR Part 11

SUB PART B – ELECTRONIC RECORDS

11.10 Controls for closed systems	
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records	Validation is clearly intended to be on a project basis. Eurotherm® has a long history of projects successfully validated to GAMP standards. Eurotherm offer assistance in validating products to GAMP guidelines. Log files which include logged process data, report data, and audit trail (alarms and events, operator notes, recipe actions, batch actions, etc) are in binary, compressed and checksumed format proprietary to Eurotherm. Details are not published. Invalid data records are rejected by Review. Review does not offer the facility to modify such records.
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.	Complete and accurate copies of logged process data, report data, and embedded audit trail are available on screen or printed out through the use of the Review package. Complete and accurate electronic copies of logged process data, report data and embedded audit trail are available by copying the raw data files, by importing to Excel, or by setting up a 'pdf printer' (requires adobe acrobat or similar) in order to export graphs in pdf format.
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	Data is Logged to removable media, via a USB port. Once removed archiving of files and backup strategy is the responsibility of the user.
(d) Limiting system access to authorized individuals.	User based security allows individuals to be granted access according to their authority level.

SUB PART B – ELECTRONIC RECORDS (continued)

11.10 Controls for closed systems (continued)	
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	Secure (embedded in the binary history file), computer generated, time-stamped runtime audit trail of batch stop/start, alarm acknowledgments, logins, recipe download, parameter changes. Record changes do not obscure previous data. Audit trail is embedded in the history file so guaranteeing retention alongside the records and availability for review / copying.
(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.	Sequencing of steps can be enforced via sequence function charts, operator messages/prompts and interlocks. The specifics are down to configuration.
(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.	Individual password protected user accounts. Each user account is allocated to a user group which determines the levels of authority within the system.
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	System errors and input channel status can be configured to be alarmed and logged automatically. Various methods to ensure a valid format of operator entered data are available.
(i) Determination that persons who develop, maintain, or use electronic record/ electronic signature systems have the education, training, and experience to perform their assigned tasks.	Procedural
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.	Procedural
(k) Use of appropriate controls over systems documentation including: **(1)** Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance. **(2)** Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.	Procedural

11.30 Controls for open systems	Not Applicable
Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in Sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality	The product is targeted at use in closed systems.

11.50 Signature Manifestations	
(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following: **(1)** The printed name of the signer; **(2)** The date and time when the signature was executed; and **(3)** The meaning (such as review, approval, responsibility, or authorship) associated with the signature.	Signed records contain unique user ID, date and time, meaning. Meaning includes signed / authorised plus an operator entered note plus automatically generated action type (eg recipe download, alarm ack, message text responded to).
(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout.	Name (ID), timestamp and meaning are all embedded in the binary format history file.

SUB PART B – ELECTRONIC RECORDS (continued)

11.70 Signature/Record Linking	
Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.	Signature manifestation is embedded in the binary format history file. For hybrid systems, prints created via review for handwritten signature will always contain timestamp details which permit re-creation from the original data.

SUB PART C – ELECTRONIC SIGNATURES

11.100 General requirements	
(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	The product ensures that no two user accounts have the same username. Deleted user ID's cannot be re-created.
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.	Procedural
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures. **(1)** The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857. **(2)** Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.	Procedural

11.200 Electronic signature components and control	
(a) Electronic signatures that are not based upon biometrics shall: **(1)** Employ at least two distinct identification components such as an identification code and password. **(i)** When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual. **(ii)** When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.	Requires re-entry of user ID and password during a signing. Both components will be required for all signings.
(2) Be used only by their genuine owners; and	Users can change their own passwords and no read access to passwords is provided. It is also possible to have logins time out after a set period of inactivity; to limit the number of login retries before an account is disabled; to set a minimum length for passwords; and to force password expiry after a set number of days.
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	Users can change their own passwords and no read access to passwords is provided. So, unless one user tells another their password, it is impossible to commit fraud without an audit trail of that fraud being left.
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.	Not applicable.

SUB PART C – ELECTRONIC SIGNATURES (continued)

11.300 Controls for identification codes/passwords	
Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:	
(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	User names are forced to be unique provided that the retired accounts doesn't exceed the maximum.
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).	It is possible to force password expiry after a set number of days. If a user leaves, their account can be retired and the user ID will remain within the uniqueness checks.
(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.	Procedural - Compromised accounts can be disabled. On loss of password, the administrator may set a new password for an account which the account holder should then immediately replace by a password of their own.
(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.	It is possible to have logins time out after a set period of inactivity; to limit the number of login retries before an account is disabled; to set a minimum length for passwords; and to force password expiry after a set number of days. Failed logins that disable accounts are detailed in the Audit Trail within the instrument.
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.	Procedural

6000

SERIES

6000 Series Recorders and 21 CFR Part 11

SUB PART B – ELECTRONIC RECORDS

11.10 Controls for closed systems	
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	Eurotherm® offer assistance in validating products to GAMP guidelines. Recorded files are in binary, compressed and check-summed format proprietary to Eurotherm. Details are not published. The viewing tool rejects invalid/altered (ie incorrectly check-summed) records. Extensive testing is carried out by Eurotherm Ltd, an ISO 9000 approved company. Validation (and maintenance of the validated state) is further supported by automatic incrementing of configuration / security version numbers each time a change is saved. These numbers are stored to the audit trail both on power up and on start of batch. They are also available as 'maths' functions to allow them to be trended if the customer requires this.
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.	Complete and accurate copies on screen or printed out are available through the use of the Review package. Complete and accurate electronic copies are available by copying the raw data files or by setting up a 'pdf printer' (requires adobe acrobat or similar) in order to export graphs in pdf format. The product also supports direct connection of an ASCII printer to which values, messages and reports can be logged. *(6100A/6180A only)*
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	On the recorder, files are held internally in Flash then archived to Removable media and/or via a network to an FTP server. Data can also be periodically pulled from the product using Review. Once data has left the recorder, the media it is stored on and backup strategy is the responsibility of the user.

SUB PART B – ELECTRONIC RECORDS (continued)

11.10 Controls for closed systems (continued)	
(d) Limiting system access to authorised individuals.	Individual password protected user accounts.
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	Secure (embedded in the binary history file), computer generated, time-stamped runtime audit trail of batch stop/start, alarm acknowledgements, logins, signature details, configuration changes. Record changes do not obscure previous data. Audit trail is embedded in the history file so guaranteeing retention alongside the records and availability for review/ copying. Time synchronisation is available via SNTP.
(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.	Interlocks can be achieved using the product configuration and relay outputs. The specifics are down to configuration. Pre-defined messages can be configured to prompt an operator for data. Operator can enter data via (signed) operator notes.
(g) Use of authority checks to ensure that only authorised individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.	Individual password protected user accounts. Each user can have a unique set of Access permissions or privileges to customise what they can do to the product.
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	System errors and input channel status are logged. Individual accounts can have remote access disabled in order to force changes to be made at the recorder.
(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.	Procedural
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.	Procedural
(k) Use of appropriate controls over systems documentation including: (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance. (2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.	Procedural

11.30 Controls for open systems	
Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in Sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.	The product is targeted at use in closed systems. However, data stored is encrypted and passwords can be configured for use on all remote access. With appropriate external systems/procedures the product may be used in an open system.

11.50 Signature Manifestations	
(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following: (1) The printed name of the signer; (2) The date and time when the signature was executed; and (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.	Signed records contain printed name (ID), date and time and meaning. Meaning includes signed/authorised plus an automatically generated type (eg 'config' for a configuration change) plus an operator entered note.

11.50 Signature Manifestations (continued)	
(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).	Name (ID), timestamp and meaning are all embedded in the binary format history file.

11.70 Signature / Record Linking	
Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.	Signature manifestation is embedded in the binary format history file. For hybrid systems, prints created via review for handwritten signature will always contain timestamp details which permit re-creation from the original data.

SUB PART C - ELECTRONIC SIGNATURES

11.100 General requirements	
(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	The product complies with this requirement by ensuring that no two user accounts have the same user name. Expired accounts may remain in the system and disabled. The number of user accounts is not limited within the software.
(b) Before an organisation establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organisation shall verify the identity of the individual.	Procedural
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures. (1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857. (2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.	Procedural

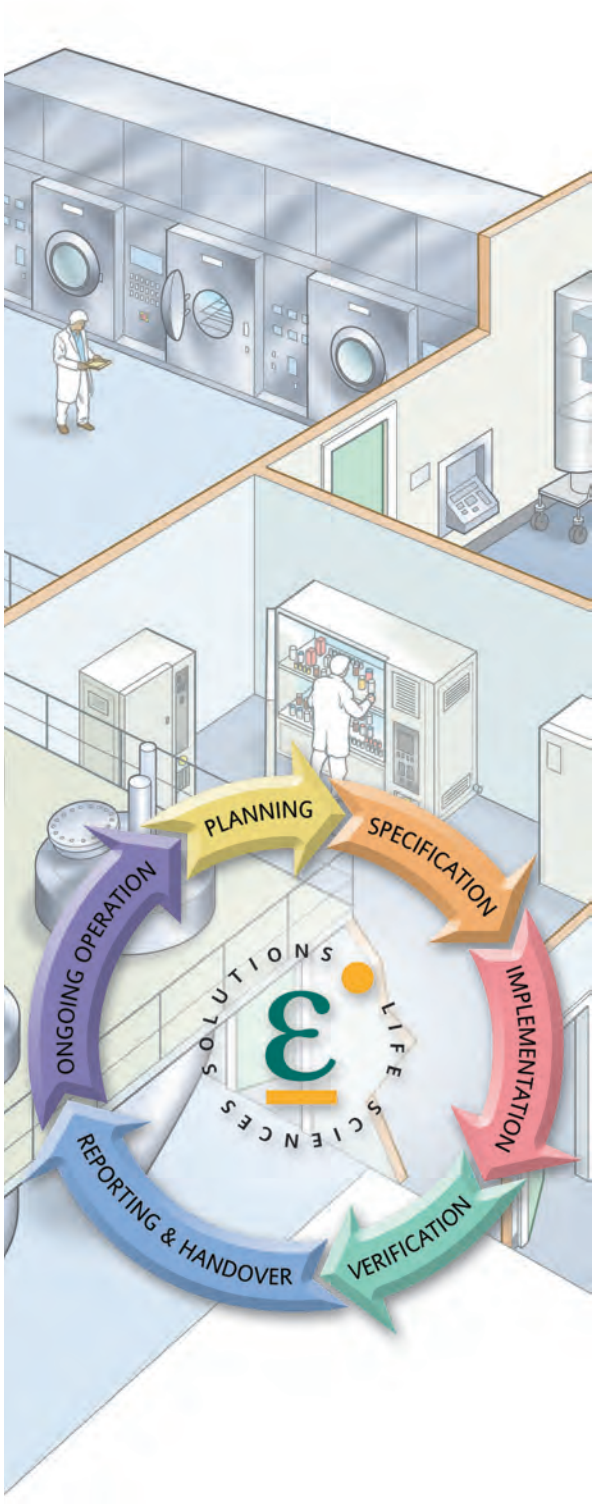
11.200 Electronic signature components and controls	
(a) Electronic signatures that are not based upon biometrics shall:.	
(1) Employ at least two distinct identification components such as an identification code and password. (i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual. (ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.	Requires re-entry of user ID and password during a signing. Both components will be required for all signings.
(2) Be used only by their genuine owners; and	Users can change their own passwords and no read access to passwords is provided. It is also possible to have logins time out after a set period of inactivity; to limit the number of login retries before an account is disabled; to set a minimum length for passwords; and to force password expiry after a set number of days.

SUB PART C – ELECTRONIC SIGNATURES (continued)

11.200 Electronic signature components and controls (continued)	
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	Users can change their own passwords and no read access to passwords is provided. So, unless one user tells another their password, it is impossible to commit fraud without an audit trail of that fraud being left. It is further possible to force system administrator changes for user accounts to be authorised by a second individual.
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.	Not applicable.

11.300 Controls for identification codes/passwords	
Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:	
(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	Providing user accounts are not deleted then all user names are forced to be unique.
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).	It is possible to force password expiry after a set number of days. If a user leaves, their account can be disabled.
(c) Following loss management procedures to electronically deauthorise lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.	Procedural – compromised accounts can be disabled. On loss of password, the administrator may set a new password for an account which the account holder should then immediately replace by a password of their own.
(d) Use of transaction safeguards to prevent unauthorised use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorised use to the system security unit, and, as appropriate, to organisational management.	It is possible to have logins time out after a set period of inactivity; to limit the number of login retries before an account is disabled; to set a minimum length for passwords; and to force password expiry after a set number of days. Failed logins that disable accounts are detailed in the Audit Trail within the instrument. This event can also be used to drive a relay to operate a remote alarm if required. *(Over Comms with 6100XIO/6180XIO)*
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorised manner.	Procedural

Life Sciences CATALOGUE



EUROTHERM ENGINEERING SERVICES

Details of Eurotherms Customer Service

- Response Services
- Performance Services
- Lifetime Services

Eurotherm Engineering Services

Eurotherm Services

...the service you need, where you need it, when you need it

For over 30 years Eurotherm have provided outstanding levels of customer service. During the 1960s and 70s, this was focused mainly on applying emerging technologies to achieve more accurate process control than was previously possible. In the 1980s and 90s, microprocessor control enabled integration techniques which required strong engineering support. Today, we continue to support our customers needs for improved up-time, improved product quality and lower manufacturing costs.

To ensure that our customers get the support they need, our service division has been identified three main areas of services: Response Services, Lifetime Services and Performance Services. The different products within these groups will meet the specific need at that time, from an engineer on the help-desk during working hours to an engineer attending site in the early hours of the morning.

- **On-site call-out**
- **Service Centre for rapid repairs**
- **Certified courses on site or in our purpose built training centre**
- **Up to 5-year warranty for instrumentation**
- **Service agreements with 8-hour response and fixed costs**
- **Calibration of any manufacturer's instrumentation on site.**
- **Spares rental service**
- **Process optimisation**
- **Archiving of process data**

RESPONSE SERVICES

These services provide solutions to immediate needs. They include local Service Centre, Field Service Engineers, the Help-desk and Technical Support. All of these resources are available to any Eurotherm customer, even without a maintenance contract. Service requests can be handled by the sales office who will prepare quotations, raise orders and schedule an engineer visit.

PERFORMANCE SERVICES

A 'business as usual' approach is not enough in today's competitive business environment. Simply maintaining existing plant and equipment to perform at original levels does not help you keep pace with changing market conditions. Our Performance Services team will work with you to improve your process to benefit your business. Customer needs vary, and no single solution will be the optimum for all customers, so using our long experience across many industries we can improve your control and monitoring applications to maintain your competitive edge.

LIFETIME SERVICES

Eurotherm customers are not left to fend for themselves after purchase. Throughout the lifetime of the product a range of services are available, to improve performance, retain regulatory compliance, or maintain high levels of 'up time'. These lifetime services include calibration, training, maintenance contracts and equipment warranties. While calibration and maintenance are the best known annual services, in addition many customers require routine training, or electronic back up of process control data off site. To improve budgeting and cost control, all of these services can be wrapped into an agreed annual service charge.

RESPONSE SERVICES

- **Highly trained engineers to solve technical queries**
- **Resolution of configuration and application issues**
- **Dedicated time by the most appropriate specialist**
- **Refurbishment not just repair**
- **12 month warranty for repairs**
- **7 day turnaround**
- **Country-wide service coverage**
- **Commissioning, repair, upgrades and training**

Service Centre

Situated within our manufacturing facility, the Service Centre provides a great deal more than a repair facility, All returned instruments are thoroughly refurbished and tested to ensure on-going reliability. Manufacturing improvements made since the product was originally shipped are also implemented. Any instrument that is still currently manufactured will be repaired under our fixed price repair scheme and returned with a 12-month warranty covering the entire product. Products that are obsolete may still be repairable using a combination of new and recycled parts.

Field Service

Our field service team provide much more than an on-site breakdown service. We are also able to assist with commissioning, training, process improvement and routine maintenance. Each engineer has been factory trained, provided with tested and verified calibration equipment, and also carries an extensive range of both spares and new instrumentation.

Help Desk

Our customer help desk facility provides technical telephone support during office hours. It is staffed only by engineers who have many years of experience. Typically, the service answers specification and configuration queries on Eurotherm products and systems. We can also offer telephone support for software products to contract customers.

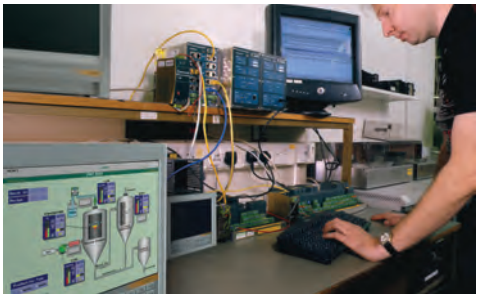
Technical Support

During commissioning or upgrade, a small amount of technical support by our engineers could save your own staff a great deal of time. Our Technical Support team can also provide additional application advice over the phone or by email. This service is available to you by the hour or by the day, and additional time can be 'banked' for future requirements. This is in addition to technical support time 'built-in' to many Eurotherm products at the time of purchase.

Comprehensive cover to suit your business requirements

PERFORMANCE SERVICES

- **Improved productivity**
- **Reduced costs**
- **Shorter cycle times**
- **Benchmark the system for performance evaluation**
- **Identify bottlenecks and provide solutions**
- **Determine network capacity for future expansion**
- **Document the network architecture for analysis**



Process Optimisation

Most businesses are driving down hard on costs and striving to improve performance. We can play a role in this process by bringing experienced engineers onto site, auditing the process and identifying possible improvements. Monitoring equipment can be installed to understand performance and costs, to create a baseline upon which the improvements can be measured. The solutions will range from simple enhancements, re-commissioning or possibly taking a completely fresh approach to the control solution. Typically this work is only completed when new projects are undertaken but we believe it can improve the productivity of plant by applying the experience of our engineers.

Network Analysis

Networks are the back bone of today's control and monitoring systems, transmitting process data between devices, local controllers and supervisory systems. Their failure can clearly have a serious impact on plant systems. Using specialist equipment, our engineers will create a report detailing the physical and electrical qualities of the network. The quality and utilisation performance, capacity and architecture will be measured and assessed. Along with physical failures, bottlenecks and the overall capacity of the system will be identified. This analysis will result in a clearer understanding of your network, reducing downtime and improving performance.

A measurable improvement

Give your process optimum performance

LIFETIME SERVICES

- **Factory trained engineers**
- **Configuration and Installation**
- **Commissioning**
- **Training**
- **Compliance with customer requirements**
- **Compliance with regulations**
- **Compliance with equipment specification**
- **Comprehensive cover plans**
- **Guaranteed response times**
- **Fixed costs**
- **UKAS accredited**
- **On-site calibration**

Commissioning

Our commissioning services include everything from configuring an instrument before it is dispatched, though to on-site installation and optimisation. During this process your staff can be trained on the configuration and operator routine. Our engineers can work alone, or alongside your plant engineering staff to reduce costs and enable knowledge transfer. After commissioning, electronic copies of the instrument configurations can be provided on CD for future use.

Re-furbishing existing panels to upgrade the control and acquisition equipment is becoming increasingly popular. The Eurotherm engineer will take control of the complete project including panel and wiring modifications. This can can provide a cost efficient method to gain compliance to regulatory standards like NADCAP and FDA.

Training

Industry today is subject to a constant demand to do more with less and if you're engaged in industrial automation of any sort, you'll appreciate that the right training can make a significant contribution to developing your company's competitive advantage. Through Eurotherm training, your employees from operators to engineering specialists, can develop the skills and knowledge required to maximise the results from your investment in plant and instrumentation. Eurotherm offers a range of scaleable, modular learning solutions that can be delivered at your site or at our training centre in Worthing.

Extended Warranties

Eurotherm now offers an extended warranty on new equipment, that can provide cover for up to 5 years. The warranty covers the cost of all parts and labour to repair any instrument that fails during normal use with the exception of consumable items.

Any faulty instrument returned to us will be fully repaired and returned to you within 7 days of receipt. We will not repair cosmetic damage that does not interfere with instrument functions.

Should you require an engineer to come to your site, this can be arranged at a specially reduced call-out rate. All parts and materials used by the engineer will be supplied free of charge under warranty.

Have your Process working first time, on time

Ensuring you get the best from your investment in plant and instrumentation

PEACE-OF-MIND

High integrity calibration with ISO9000 processing and record keeping

UKAS CALIBRATION 0778

On-site UKAS Accredited Service

Lifetime Service Agreements

Assured response to site, fixed costs and agreed maintenance routines are all provided with Lifetime Support Agreements. The customer decides the level of service for each element of the contract. Response to site can be from within 8 hours or up to next working day. Telephone support can be enhanced to 24/7 cover with optional remote diagnostic facility. Instrument warranties can be extended under the contract to provide fixed costs for maintenance. Configuration back-ups of equipment and PCs can be included to enhance up time. On site spares can be provided to ensure that instrument failure causes the least amount of plant disruption. Elements of the contract may be passed onto the next year if they are unused. The contract will clearly show the levels of support being provided and the amount of time contracted to give complete transparency to the agreement.

Calibration

Eurotherm can provide UKAS Accredited calibration certificates for a wide range of process parameters. Other parameters can be calibrated and are supplied with Eurotherm traceable calibration certificates. This service can be on-site or at the calibration laboratory. When conducted on-site, if an instrument fails calibration a loan or replacement item is supplied to minimise plant disruption. The calibration team are a specialist group of engineers within Eurotherm and are backed by a team within the factory. These teams are able to work to the wide range of regulations and procedures operated by different companies including: AMS2750, RPS953, GAMP, UKAS and ISO9000 procedures.

In addition to process equipment, the team have a specialist furnace survey package to provide the most detailed reports required. The equipment has UKAS accredited calibration systems and engineers are all trained to the different industry standards. Sample reports are available for inspection.

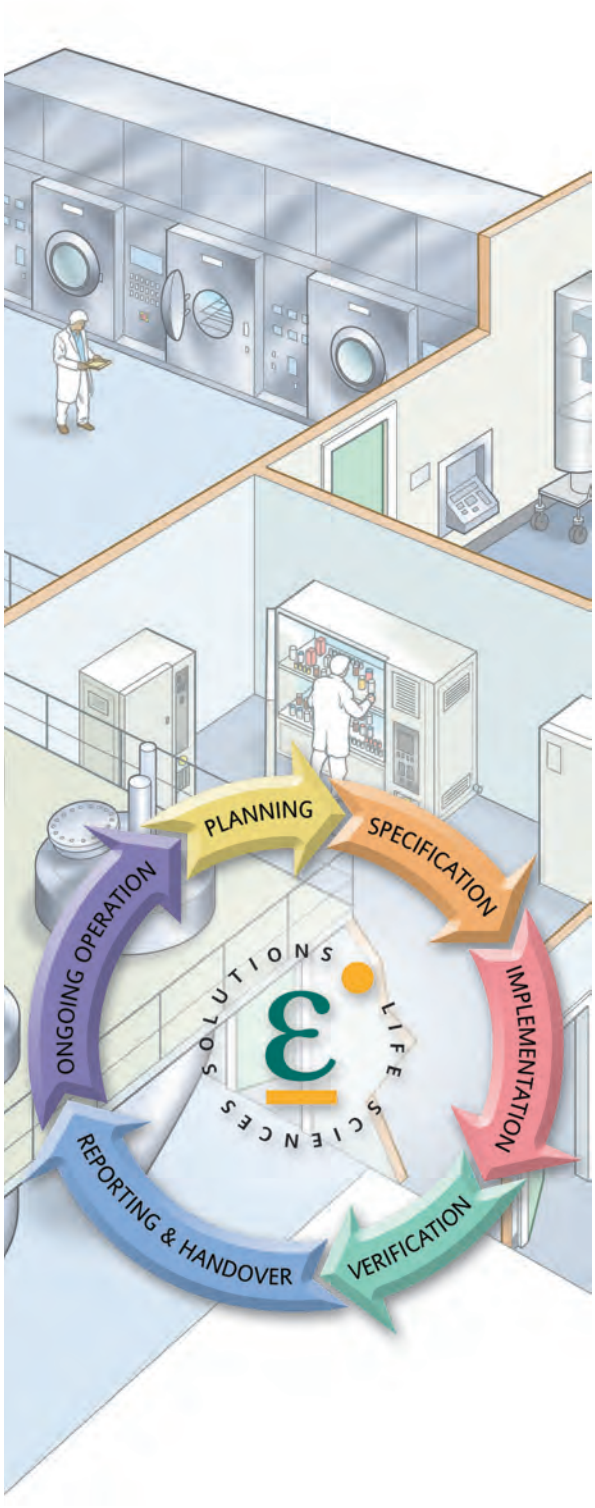
Preventative Maintenance

To maximise system availability and uptime Eurotherm have a range of onsite Preventative Maintenance services to ensure your investment is protected and operating efficiently.

This includes:
- Diagnostic performance and error checking
- Dry vacuum cleaning to remove corrosive contaminates and dust
- Replacement of filters, fans and checking fan rundown times
- Defragmentation
- Offline virus checking
- Audit and validation of spares
- Tailored service plan
- Proactive advice on hardware and software upgrade requirements

In particular the service includes Disaster recovery backups of both your DCS and the SCADA PC workstations. In the event of a hardware failure these backups ensure the spares can be up and running using a well defined and simple recovery process.

Life Sciences CATALOGUE



APPENDIX 1

Guidance for industry - FDA

- Guidance for Industry, Part 11, Electronic Record Electronic Signatures - Scope and Application
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- Guidance for Industry, Q7A Good Manufacturing Practice, Guidance for Active Pharmaceutical Ingredients
- Quality Risk management, Q9
- Guidance for Industry, Computerised Systems Used in Clinical Trials
- Guidance for Industry, Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV
- Guidance for Industry, Q1A(R2) Stability Testing of New Drug Substances and Products

The information provided in this Appendix is reprinted from the indicated source or controlling authority for the particular document.

For the latest revision of any document reproduced here please consult the relevant controlling authority.

Useful contacts:
www.fda.gov

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

Division of Drug Information, HFD-240
Center for Drug Evaluation and Research (CDER)
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/cber/guidelines.htm
Phone: the Voice Information System at 800-835-4709 or 301-827-1800
or
Communications Staff (HFV-12),
Center for Veterinary Medicine (CVM)
(Tel) 301-594-1755
http://www.fda.gov/cvm/guidance/guidance.html
or
Division of Small Manufacturers Assistance (HFZ-220)
http://www.fda.gov/cdrh/ggpmain.html
Manufacturers Assistance Phone Number: 800.638.2041 or 301.443.6597
Internt'l Staff Phone: 301.827.3993
or
Center for Food Safety and Applied Nutrition (CFSAN)
http://www.cfsan.fda.gov/~dms/guidance.html.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
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Guidance for Industry[1]
Part 11, Electronic Records; Electronic Signatures — Scope and Application

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to describe the Food and Drug Administration's (FDA's) current thinking regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11).[2]

This document provides guidance to persons who, in fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA,[3] have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as *predicate rules.*

[1] This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in consultation with the other Agency centers and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] 62 FR 13430

[3] These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR Part 211), the Quality System regulation (21 CFR Part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR Part 58).

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics,[4] FDA is re-examining part 11 as it applies to all FDA regulated products. We anticipate initiating rulemaking to change part 11 as a result of that re-examination. This guidance explains that we will narrowly interpret the scope of part 11. While the re-examination of part 11 is under way, we intend to exercise enforcement discretion with respect to certain part 11 requirements. That is, we do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.

In addition, we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.

Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:

[4] See *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* at www.fda.gov/oc/guidance/gmp.html.

- *21 CFR Part 11; Electronic Records; Electronic Signatures, Validation*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the *Federal Register* of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*. We had decided we wanted to minimize industry time spent reviewing and commenting on the draft guidance when that draft guidance may no longer represent our approach under the CGMP initiative. Then, in the *Federal Register* of February 25, 2003 (68 FR 8775), we announced the withdrawal of the part 11 draft guidance documents on validation, glossary of terms, time stamps,[5] maintenance of electronic records, and CPG 7153.17. We received valuable public comments on these draft guidances, and we plan to use that information to help with future decision-making with respect to part 11. We do not intend to re-issue these draft guidance documents or the CPG.

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period.

III. DISCUSSION

A. Overall Approach to Part 11 Requirements

[5] Although we withdrew the draft guidance on time stamps, our current thinking has not changed in that when using time stamps for systems that span different time zones, we do not expect you to record the signer's local time. When using time stamps, they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly; we are now clarifying that fewer records will be considered subject to part 11.
- For those records that remain subject to part 11, we intend to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- We will enforce all predicate rule requirements, including predicate rule record and recordkeeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach – Scope of Part 11

1. Narrow Interpretation of Scope

We understand that there is some confusion about the scope of part 11. Some have understood the scope of part 11 to be very broad. We believe that some of those broad interpretations could

lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the Agency intends to interpret the scope of part 11 narrowly.

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

2. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format*. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records.

  We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.

- Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format*, and that *are relied on to perform regulated activities*.

  In some cases, actual business practices may dictate whether you are *using* electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be *using* the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.

  Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used

in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. *approved*, *reviewed*, and *verified*).

C. Approach to Specific Part 11 Requirements

1. Validation

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Although persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)), this guidance should not be read to impose any additional requirements for validation.

We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system.

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.

For further guidance on validation of computerized systems, see FDA's guidance for industry and FDA staff *General Principles of Software Validation* and also industry guidance such as the *GAMP 4 Guide* (See References).

2. Audit Trail

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and

reliability of the records.[6] We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

3. Legacy Systems[7]

The Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below.

This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was operational before the effective date.
- The system met all applicable predicate rule requirements before the effective date.
- The system currently meets all applicable predicate rule requirements.
- You have documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).

If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied to Part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

4. Copies of Records

The Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10 (b) and any corresponding requirement in §11.30). You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you are subject to inspection in accordance with predicate rules (e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)).

We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML)

[6] Various guidance documents on information security are available (see References).

[7] In this guidance document, we use the term *legacy system* to describe systems already in operation before the effective date of part 11.

In each case, we recommend that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

5. Record Retention

The Agency intends to exercise enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10 (c) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements for record retention and availability (e.g., §§ 211.180(c),(d), 108.25(g), and 108.35(h)).

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can co-exist (i.e., a hybrid[8] situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

[8] Examples of hybrid situations include combinations of paper records (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

IV. REFERENCES

Food and Drug Administration References

1. *Glossary of Computerized System and Software Development Terminolo*gy (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, FDA 1995) (http://www. fda.gov/ora/inspect_ref/igs/gloss.html)

2. *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002) (http://www.fda.gov/cdrh/comp/guidance/938.html)

3. *Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices* (FDA, Center for Devices and Radiological Health, 1999) (http://www.fda.gov/cdrh/ode/guidance/585.html)

4. *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* (FDA 2002) (http://www.fda.gov/oc/guidance/gmp.html)

Industry References

1. *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) (http://www.ispe.org/gamp/)

2. ISO/IEC 17799:2000 (BS 7799:2000) Information technology – Code of practice for information security management (ISO/IEC, 2000)

3. ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

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U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance which involve the Center for Devices and Radiological Health (CDRH), contact John F. Murray at (301) 594-4659 or email jfm@cdrh.fda.gov

For questions regarding the use or interpretation of this guidance which involve the Center for Biologics Evaluation and Research (CBER) contact Jerome Davis at (301) 827-6220 or email davis@cber.fda.gov.

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Additional copies are available from the Internet at: http://www.fda.gov/cber/guidelines.htm, by writing to CBER, Office of Communication, Training, and Manufacturers' Assistance (HFM-40), 1401 Rockville Pike, Rockville, Maryland 20852-1448, or by telephone request at 1-800-835-5709 or 301-827-1800.

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General Principles of Software Validation

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

SECTION 1. PURPOSE

This guidance outlines general validation principles that the Food and Drug Administration (FDA) considers to be applicable to the validation of medical device software or the validation of software used to design, develop, or manufacture medical devices. This final guidance document, Version 2.0, supersedes the draft document, *General Principles of Software Validation, Version 1.1*, dated June 9, 1997.

SECTION 2. SCOPE

This guidance describes how certain provisions of the medical device Quality System regulation apply to software and the agency's current approach to evaluating a software validation system. For example, this document lists elements that are acceptable to the FDA for the validation of software; however, it does not list all of the activities and tasks that must, in all instances, be used to comply with the law.

The scope of this guidance is somewhat broader than the scope of validation in the strictest definition of that term. Planning, verification, testing, traceability, configuration management, and many other aspects of good software engineering discussed in this guidance are important activities that together help to support a final conclusion that software is validated.

This guidance recommends an integration of software life cycle management and risk management activities. Based on the intended use and the safety risk associated with the software to be developed, the software developer should determine the specific approach, the combination of techniques to be used, and the level of effort to be applied. While this guidance does not recommend any specific life cycle model or any specific technique or method, it does recommend that software validation and verification activities be conducted throughout the entire software life cycle.

Where the software is developed by someone other than the device manufacturer (e.g., off-the-shelf software) the software developer may not be directly responsible for compliance with FDA regulations.

In that case, the party with regulatory responsibility (i.e., the device manufacturer) needs to assess the adequacy of the off-the-shelf software developer's activities and determine what additional efforts are needed to establish that the software is validated for the device manufacturer's intended use.

2.1. APPLICABILITY

This guidance applies to:

- Software used as a component, part, or accessory of a medical device;
- Software that is itself a medical device (e.g., blood establishment software);
- Software used in the production of a device (e.g., programmable logic controllers in manufacturing equipment); and
- Software used in implementation of the device manufacturer's quality system (e.g., software that records and maintains the device history record).

This document is based on generally recognized software validation principles and, therefore, can be applied to any software. For FDA purposes, this guidance applies to any software related to a regulated medical device, as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) and by current FDA software and regulatory policy. This document does not specifically identify which software is or is not regulated.

2.2. AUDIENCE

This guidance provides useful information and recommendations to the following individuals:

- Persons subject to the medical device Quality System regulation
- Persons responsible for the design, development, or production of medical device software
- Persons responsible for the design, development, production, or procurement of automated tools used for the design, development, or manufacture of medical devices or software tools used to implement the quality system itself
- FDA Investigators
- FDA Compliance Officers
- FDA Scientific Reviewers

2.3. THE LEAST BURDENSOME APPROACH

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider

your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at:

http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html.

2.4. REGULATORY REQUIREMENTS FOR SOFTWARE VALIDATION

The FDA's analysis of 3140 medical device recalls conducted between 1992 and 1998 reveals that 242 of them (7.7%) are attributable to software failures. Of those software related recalls, 192 (or 79%) were caused by software defects that were introduced when changes were made to the software after its initial production and distribution. Software validation and other related good software engineering practices discussed in this guidance are a principal means of avoiding such defects and resultant recalls.

Software validation is a requirement of the Quality System regulation, which was published in the Federal Register on October 7, 1996 and took effect on June 1, 1997. (See Title 21 Code of Federal Regulations (CFR) Part 820, and 61 Federal Register (FR) 52602, respectively.) Validation requirements apply to software used as components in medical devices, to software that is itself a medical device, and to software used in production of the device or in implementation of the device manufacturer's quality system.

Unless specifically exempted in a classification regulation, any medical device software product developed after June 1, 1997, regardless of its device class, is subject to applicable design control provisions. (See of 21 CFR §820.30.) This requirement includes the completion of current development projects, all new development projects, and all changes made to existing medical device software. Specific requirements for validation of device software are found in 21 CFR §820.30(g). Other design controls, such as planning, input, verification, and reviews, are required for medical device software. (See 21 CFR §820.30.) The corresponding documented results from these activities can provide additional support for a conclusion that medical device software is validated.

Any software used to automate any part of the device production process or any part of the quality system must be validated for its intended use, as required by 21 CFR §820.70(i). This requirement applies to any software used to automate device design, testing, component acceptance, manufacturing, labeling, packaging, distribution, complaint handling, or to automate any other aspect of the quality system.

In addition, computer systems used to create, modify, and maintain electronic records and to manage electronic signatures are also subject to the validation requirements. (See 21 CFR §11.10(a).) Such computer systems must be validated to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

Software for the above applications may be developed in-house or under contract. However, software is frequently purchased off-the-shelf for a particular intended use. All production and/or quality system software, even if purchased off-the-shelf, should have documented requirements that fully define its intended use, and information against which testing results and other evidence can be compared, to show that the software is validated for its intended use.

The use of off-the-shelf software in automated medical devices and in automated manufacturing and quality system operations is increasing. Off-the-shelf software may have many capabilities, only a few of which are needed by the device manufacturer. Device manufacturers are responsible for the adequacy of the software used in their devices, and used to produce devices. When device manufacturers purchase "off-the-shelf" software, they must ensure that it will perform as intended in their chosen application. For off-the-shelf software used in manufacturing or in the quality system, additional guidance is included in Section 6.3 of this document. For device software, additional useful information may be found in FDA's *Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices*.

2.4. QUALITY SYSTEM REGULATION VS PRE-MARKET SUBMISSIONS

This document addresses Quality System regulation issues that involve the implementation of software validation. It provides guidance for the management and control of the software validation process. The management and control of the software validation process should not be confused with any other validation requirements, such as process validation for an automated manufacturing process.

Device manufacturers may use the same procedures and records for compliance with quality system and design control requirements, as well as for pre-market submissions to FDA. This document does not cover any specific safety or efficacy issues related to software validation. Design issues and documentation requirements for pre-market submissions of regulated software are not addressed by this document. Specific issues related to safety and efficacy, and the documentation required in pre-market submissions, should be addressed to the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH) or to the Office of Blood Research and Review, Center for Biologics Evaluation and Research (CBER). See the references in Appendix A for applicable FDA guidance documents for pre-market submissions.

SECTION 3. CONTEXT FOR SOFTWARE VALIDATION

Many people have asked for specific guidance on what FDA expects them to do to ensure compliance with the Quality System regulation with regard to software validation. Information on software validation presented in this document is not new. Validation of software, using the principles and tasks listed in Sections 4 and 5, has been conducted in many segments of the software industry for well over 20 years.

Due to the great variety of medical devices, processes, and manufacturing facilities, it is not possible to state in one document all of the specific validation elements that are applicable. However, a general application of several broad concepts can be used successfully as guidance for software validation. These broad concepts provide an acceptable framework for building a comprehensive approach to software validation. Additional specific information is available from many of the references listed in Appendix A.

3.1. DEFINITIONS AND TERMINOLOGY

Unless defined in the Quality System regulation, or otherwise specified below, all other terms used in this guidance are as defined in the current edition of the FDA *Glossary of Computerized System and Software Development Terminology*.

The medical device Quality System regulation (21 CFR 820.3(k)) defines "**establish**" to mean "define, document, and implement." Where it appears in this guidance, the words "establish" and "established" should be interpreted to have this same meaning.

Some definitions found in the medical device Quality System regulation can be confusing when compared to commonly used terminology in the software industry. Examples are requirements, specification, verification, and validation.

3.1.1 Requirements and Specifications

While the Quality System regulation states that design input requirements must be documented, and that specified requirements must be verified, the regulation does not further clarify the distinction between the terms "requirement" and "specification." A **requirement** can be any need or expectation for a system or for its software. Requirements reflect the stated or implied needs of the customer, and may be market-based, contractual, or statutory, as well as an organization's internal requirements. There can be many different kinds of requirements (e.g., design, functional, implementation, interface, performance, or physical requirements). Software requirements are typically derived from the system requirements for those aspects of system functionality that have been allocated to software. Software requirements are typically stated in functional terms and are defined, refined, and updated as a development project progresses. Success in accurately and completely documenting software requirements is a crucial factor in successful validation of the resulting software.

A **specification** is defined as "a document that states requirements." (See 21 CFR §820.3(y).) It may refer to or include drawings, patterns, or other relevant documents and usually indicates the means and the criteria whereby conformity with the requirement can be checked. There are many different kinds of written specifications, e.g., system requirements specification, software requirements specification, software design specification, software test specification, software integration specification, etc. All of these documents establish "specified requirements" and are design outputs for which various forms of verification are necessary.

3.1.2 Verification and Validation

The Quality System regulation is harmonized with *ISO 8402*:1994, which treats "verification" and "validation" as separate and distinct terms. On the other hand, many software engineering journal articles and textbooks use the terms "verification" and "validation" interchangeably, or in some cases refer to software "verification, validation, and testing (VV&T)" as if it is a single concept, with no distinction among the three terms.

Software verification provides objective evidence that the design outputs of a particular phase of the software development life cycle meet all of the specified requirements for that phase. Software verification looks for consistency, completeness, and correctness of the software and its supporting documentation, as it is being developed, and provides support for a subsequent conclusion that software is validated. Software testing is one of many verification activities intended to confirm that software development output meets its input requirements. Other verification activities include various static and dynamic analyses, code and document inspections, walkthroughs, and other techniques.

Software validation is a part of the design validation for a finished device, but is not separately defined in the Quality System regulation. For purposes of this guidance, FDA considers software validation to be "**confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.**" In practice, software validation activities may occur both during, as well as at the end of the software development life cycle to ensure that all requirements have been fulfilled. Since software is usually part of a larger hardware system, the validation of software typically includes evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. A conclusion that software is validated is highly dependent upon comprehensive software testing, inspections, analyses, and other verification tasks performed at each stage of the software development life cycle. Testing of device software functionality in a simulated use environment, and user site testing are typically included as components of an overall design validation program for a software automated device.

Software verification and validation are difficult because a developer cannot test forever, and it is hard to know how much evidence is enough. In large measure, software validation is a matter of developing a "level of confidence" that the device meets all requirements and user expectations for the software automated functions and features of the device. Measures such as defects found in specifications documents, estimates of defects remaining, testing coverage, and other techniques are all used to

develop an acceptable level of confidence before shipping the product. The level of confidence, and therefore the level of software validation, verification, and testing effort needed, will vary depending upon the safety risk (hazard) posed by the automated functions of the device. Additional guidance regarding safety risk management for software may be found in Section 4 of FDA's *Guidance for the Content of Pre-market Submissions for Software Contained in Medical Devices*, and in the international standards *ISO/IEC 14971-1* and *IEC 60601-1-4* referenced in Appendix A.

3.1.3 IQ/OQ/PQ

For many years, both FDA and regulated industry have attempted to understand and define software validation within the context of process validation terminology. For example, industry documents and other FDA validation guidance sometimes describe user site software validation in terms of installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Definitions of these terms and additional information regarding IQ/OQ/PQ may be found in FDA's *Guideline on General Principles of Process Validation*, dated May 11, 1987, and in FDA's *Glossary of Computerized System and Software Development Terminology*, dated August 1995.

While IQ/OQ/PQ terminology has served its purpose well and is one of many legitimate ways to organize software validation tasks at the user site, this terminology may not be well understood among many software professionals, and it is not used elsewhere in this document. However, both FDA personnel and device manufacturers need to be aware of these differences in terminology as they ask for and provide information regarding software validation.

3.2. SOFTWARE DEVELOPMENT AS PART OF SYSTEM DESIGN

The decision to implement system functionality using software is one that is typically made during system design. Software requirements are typically derived from the overall system requirements and design for those aspects in the system that are to be implemented using software. There are user needs and intended uses for a finished device, but users typically do not specify whether those requirements are to be met by hardware, software, or some combination of both. Therefore, software validation must be considered within the context of the overall design validation for the system.

A documented requirements specification represents the user's needs and intended uses from which the product is developed. A primary goal of software validation is to then demonstrate that all completed software products comply with all documented software and system requirements. The correctness and completeness of both the system requirements and the software requirements should be addressed as part of the design validation process for the device. Software validation includes confirmation of conformance to all software specifications and confirmation that all software requirements are traceable to the system specifications. Confirmation is an important part of the overall design validation to ensure that all aspects of the medical device conform to user needs and intended uses.

3.3. SOFTWARE IS DIFFERENT FROM HARDWARE

While software shares many of the same engineering tasks as hardware, it has some very important differences. For example:

- The vast majority of software problems are traceable to errors made during the design and development process. While the quality of a hardware product is highly dependent on design, development and manufacture, the quality of a software product is dependent primarily on design and development with a minimum concern for software manufacture. Software manufacturing consists of reproduction that can be easily verified. It is not difficult to manufacture thousands of program copies that function exactly the same as the original; the difficulty comes in getting the original program to meet all specifications.

- One of the most significant features of software is branching, i.e., the ability to execute alternative series of commands, based on differing inputs. This feature is a major contributing factor for another characteristic of software – its complexity. Even short programs can be very complex and difficult to fully understand.

- Typically, testing alone cannot fully verify that software is complete and correct. In addition to testing, other verification techniques and a structured and documented development process should be combined to ensure a comprehensive validation approach.

- Unlike hardware, software is not a physical entity and does not wear out. In fact, software may improve with age, as latent defects are discovered and removed. However, as software is constantly updated and changed, such improvements are sometimes countered by new defects introduced into the software during the change.

- Unlike some hardware failures, software failures occur without advanced warning. The software's branching that allows it to follow differing paths during execution, may hide some latent defects until long after a software product has been introduced into the marketplace.

- Another related characteristic of software is the speed and ease with which it can be changed. This factor can cause both software and non-software professionals to believe that software problems can be corrected easily. Combined with a lack of understanding of software, it can lead managers to believe that tightly controlled engineering is not needed as much for software as it is for hardware. In fact, the opposite is true. **Because of its complexity, the development process for software should be even more tightly controlled than for hardware, in order to prevent problems that cannot be easily detected later in the development process**.

- Seemingly insignificant changes in software code can create unexpected and very significant problems elsewhere in the software program. The software development process should be sufficiently well planned, controlled, and documented to detect and correct unexpected results from software changes.

- Given the high demand for software professionals and the highly mobile workforce, the software personnel who make maintenance changes to software may not have been involved in the original software development. Therefore, accurate and thorough documentation is essential.

- Historically, software components have not been as frequently standardized and interchangeable as hardware components. However, medical device software developers are beginning to use component-based development tools and techniques. Object-oriented methodologies and the use of off-the-shelf software components hold promise for faster and less expensive software development. However, component-based approaches require very careful attention during integration. Prior to integration, time is needed to fully define and develop reusable software code and to fully understand the behavior of off-the-shelf components.

For these and other reasons, software engineering needs an even greater level of managerial scrutiny and control than does hardware engineering.

3.4. BENEFITS OF SOFTWARE VALIDATION

Software validation is a critical tool used to assure the quality of device software and software automated operations. Software validation can increase the usability and reliability of the device, resulting in decreased failure rates, fewer recalls and corrective actions, less risk to patients and users, and reduced liability to device manufacturers. Software validation can also reduce long term costs by making it easier and less costly to reliably modify software and revalidate software changes. Software maintenance can represent a very large percentage of the total cost of software over its entire life cycle. An established comprehensive software validation process helps to reduce the long-term cost of software by reducing the cost of validation for each subsequent release of the software.

3.5 DESIGN REVIEW

Design reviews are documented, comprehensive, and systematic examinations of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems. While there may be many informal technical reviews that occur within the development team during a software project, a formal design review is more structured and includes participation from others outside the development team. Formal design reviews may reference or include results from other formal and informal reviews. Design reviews may be conducted separately for the software, after the software is integrated with the hardware into the system, or both. Design reviews should include examination of development plans, requirements specifications, design specifications, testing plans and procedures, all other documents and activities associated with the project, verification results from each stage of the defined life cycle, and validation results for the overall device.

Design review is a primary tool for managing and evaluating development projects. For example, formal design reviews allow management to confirm that all goals defined in the software validation plan have

been achieved. The Quality System regulation requires that at least one formal design review be conducted during the device design process. However, it is recommended that multiple design reviews be conducted (e.g., at the end of each software life cycle activity, in preparation for proceeding to the next activity). Formal design review is especially important at or near the end of the requirements activity, before major resources have been committed to specific design solutions. Problems found at this point can be resolved more easily, save time and money, and reduce the likelihood of missing a critical issue.

Answers to some key questions should be documented during formal design reviews. These include:

- Have the appropriate tasks and expected results, outputs, or products been established for each software life cycle activity?

- Do the tasks and expected results, outputs, or products of each software life cycle activity:

  - ✓ Comply with the requirements of other software life cycle activities in terms of correctness, completeness, consistency, and accuracy?

  - ✓ Satisfy the standards, practices, and conventions of that activity?

  - ✓ Establish a proper basis for initiating tasks for the next software life cycle activity?

SECTION 4. PRINCIPLES OF SOFTWARE VALIDATION

This section lists the general principles that should be considered for the validation of software.

4.1. REQUIREMENTS

A documented software requirements specification provides a baseline for both validation and verification. The software validation process cannot be completed without an established software requirements specification (Ref: 21 CFR 820.3(z) and (aa) and 820.30(f) and (g)).

4.2. DEFECT PREVENTION

Software quality assurance needs to focus on preventing the introduction of defects into the software development process and not on trying to "test quality into" the software code after it is written. Software testing is very limited in its ability to surface all latent defects in software code. For example, the complexity of most software prevents it from being exhaustively tested. **Software testing is a necessary activity. However, in most cases software testing by itself is not sufficient to establish confidence that the software is fit for its intended use.** In order to establish that confidence, software developers should use a mixture of methods and techniques to prevent software errors and to detect software errors that do occur. The "best mix" of methods depends on many factors including the development environment, application, size of project, language, and risk.

4.3. TIME AND EFFORT

To build a case that the software is validated requires time and effort. Preparation for software validation should begin early, i.e., during design and development planning and design input. The final conclusion that the software is validated should be based on evidence collected from planned efforts conducted throughout the software lifecycle.

4.4. SOFTWARE LIFE CYCLE

Software validation takes place within the environment of an established software life cycle. The software life cycle contains software engineering tasks and documentation necessary to support the software validation effort. In addition, the software life cycle contains specific verification and validation tasks that are appropriate for the intended use of the software. This guidance does not recommend any particular life cycle models – only that they should be selected and used for a software development project.

4.5. PLANS

The software validation process is defined and controlled through the use of a plan. The software validation plan defines "what" is to be accomplished through the software validation effort. Software validation plans are a significant quality system tool. Software validation plans specify areas such as scope, approach, resources, schedules and the types and extent of activities, tasks, and work items.

4.6. PROCEDURES

The software validation process is executed through the use of procedures. These procedures establish "how" to conduct the software validation effort. The procedures should identify the specific actions or sequence of actions that must be taken to complete individual validation activities, tasks, and work items.

4.7. SOFTWARE VALIDATION AFTER A CHANGE

Due to the complexity of software, a seemingly small local change may have a significant global system impact. When any change (even a small change) is made to the software, the validation status of the software needs to be re-established. **Whenever software is changed, a validation analysis should be conducted not just for validation of the individual change, but also to determine the extent and impact of that change on the entire software system.** Based on this analysis, the software developer should then conduct an appropriate level of software regression testing to show that unchanged but vulnerable portions of the system have not been adversely affected. Design controls and appropriate regression testing provide the confidence that the software is validated after a software change.

4.8. VALIDATION COVERAGE

Validation coverage should be based on the software's complexity and safety risk – not on firm size or resource constraints. The selection of validation activities, tasks, and work items should be commensurate with the complexity of the software design and the risk associated with the use of the software for the specified intended use. For lower risk devices, only baseline validation activities may be conducted. As the risk increases additional validation activities should be added to cover the additional risk. Validation documentation should be sufficient to demonstrate that all software validation plans and procedures have been completed successfully.

4.9. INDEPENDENCE OF REVIEW

Validation activities should be conducted using the basic quality assurance precept of "independence of review." Self-validation is extremely difficult. When possible, an independent evaluation is always better, especially for higher risk applications. Some firms contract out for a third-party independent

verification and validation, but this solution may not always be feasible. Another approach is to assign internal staff members that are not involved in a particular design or its implementation, but who have sufficient knowledge to evaluate the project and conduct the verification and validation activities. Smaller firms may need to be creative in how tasks are organized and assigned in order to maintain internal independence of review.

4.10. FLEXIBILITY AND RESPONSIBILITY

Specific implementation of these software validation principles may be quite different from one application to another. The device manufacturer has flexibility in choosing how to apply these validation principles, but retains ultimate responsibility for demonstrating that the software has been validated.

Software is designed, developed, validated, and regulated in a wide spectrum of environments, and for a wide variety of devices with varying levels of risk. FDA regulated medical device applications include software that:

- Is a component, part, or accessory of a medical device;
- Is itself a medical device; or
- Is used in manufacturing, design and development, or other parts of the quality system.

In each environment, software components from many sources may be used to create the application (e.g., in-house developed software, off-the-shelf software, contract software, shareware). In addition, software components come in many different forms (e.g., application software, operating systems, compilers, debuggers, configuration management tools, and many more). The validation of software in these environments can be a complex undertaking; therefore, it is appropriate that all of these software validation principles be considered when designing the software validation process. The resultant software validation process should be commensurate with the safety risk associated with the system, device, or process.

Software validation activities and tasks may be dispersed, occurring at different locations and being conducted by different organizations. However, regardless of the distribution of tasks, contractual relations, source of components, or the development environment, the device manufacturer or specification developer retains ultimate responsibility for ensuring that the software is validated.

SECTION 5. ACTIVITIES AND TASKS

Software validation is accomplished through a series of activities and tasks that are planned and executed at various stages of the software development life cycle. These tasks may be one time occurrences or may be iterated many times, depending on the life cycle model used and the scope of changes made as the software project progresses.

5.1. SOFTWARE LIFE CYCLE ACTIVITIES

This guidance does not recommend the use of any specific software life cycle model. Software developers should establish a software life cycle model that is appropriate for their product and organization. The software life cycle model that is selected should cover the software from its birth to its retirement. Activities in a typical software life cycle model include the following:

- Quality Planning
- System Requirements Definition
- Detailed Software Requirements Specification
- Software Design Specification
- Construction or Coding
- Testing
- Installation
- Operation and Support
- Maintenance
- Retirement

Verification, testing, and other tasks that support software validation occur during each of these activities. A life cycle model organizes these software development activities in various ways and provides a framework for monitoring and controlling the software development project. Several software life cycle models (e.g., waterfall, spiral, rapid prototyping, incremental development, etc.) are defined in FDA's *Glossary of Computerized System and Software Development Terminology*, dated August 1995. These and many other life cycle models are described in various references listed in Appendix A.

5.2. TYPICAL TASKS SUPPORTING VALIDATION

For each of the software life cycle activities, there are certain "typical" tasks that support a conclusion that the software is validated. However, the specific tasks to be performed, their order of performance, and the iteration and timing of their performance will be dictated by the specific software life cycle model that is selected and the safety risk associated with the software application. For very low risk applications, certain tasks may not be needed at all. However, the software developer should at least consider each of these tasks and should define and document which tasks are or are not appropriate for

their specific application. The following discussion is generic and is not intended to prescribe any particular software life cycle model or any particular order in which tasks are to be performed.

5.2.1. Quality Planning

Design and development planning should culminate in a plan that identifies necessary tasks, procedures for anomaly reporting and resolution, necessary resources, and management review requirements, including formal design reviews. A software life cycle model and associated activities should be identified, as well as those tasks necessary for each software life cycle activity. The plan should include:

- The specific tasks for each life cycle activity;
- Enumeration of important quality factors (e.g., reliability, maintainability, and usability);
- Methods and procedures for each task;
- Task acceptance criteria;
- Criteria for defining and documenting outputs in terms that will allow evaluation of their conformance to input requirements;
- Inputs for each task;
- Outputs from each task;
- Roles, resources, and responsibilities for each task;
- Risks and assumptions; and
- Documentation of user needs.

Management must identify and provide the appropriate software development environment and resources. (See 21 CFR §820.20(b)(1) and (2).) Typically, each task requires personnel as well as physical resources. The plan should identify the personnel, the facility and equipment resources for each task, and the role that risk (hazard) management will play. A configuration management plan should be developed that will guide and control multiple parallel development activities and ensure proper communications and documentation. Controls are necessary to ensure positive and correct correspondence among all approved versions of the specifications documents, source code, object code, and test suites that comprise a software system. The controls also should ensure accurate identification of, and access to, the currently approved versions.

Procedures should be created for reporting and resolving software anomalies found through validation or other activities. Management should identify the reports and specify the contents, format, and responsible organizational elements for each report. Procedures also are necessary for the review and approval of software development results, including the responsible organizational elements for such reviews and approvals.

<u>Typical Tasks – Quality Planning</u>

- Risk (Hazard) Management Plan
- Configuration Management Plan

- Software Quality Assurance Plan
  - Software Verification and Validation Plan
    - Verification and Validation Tasks, and Acceptance Criteria
    - Schedule and Resource Allocation (for software verification and validation activities)
    - Reporting Requirements
  - Formal Design Review Requirements
  - Other Technical Review Requirements
- Problem Reporting and Resolution Procedures
- Other Support Activities

5.2.2. Requirements

Requirements development includes the identification, analysis, and documentation of information about the device and its intended use. Areas of special importance include allocation of system functions to hardware/software, operating conditions, user characteristics, potential hazards, and anticipated tasks. In addition, the requirements should state clearly the intended use of the software.

The software requirements specification document should contain a written definition of the software functions. It is not possible to validate software without predetermined and documented software requirements. Typical software requirements specify the following:

- All software system inputs;
- All software system outputs;
- All functions that the software system will perform;
- All performance requirements that the software will meet, (e.g., data throughput, reliability, and timing);
- The definition of all external and user interfaces, as well as any internal software-to-system interfaces;
- How users will interact with the system;
- What constitutes an error and how errors should be handled;
- Required response times;
- The intended operating environment for the software, if this is a design constraint (e.g., hardware platform, operating system);
- All ranges, limits, defaults, and specific values that the software will accept; and
- All safety related requirements, specifications, features, or functions that will be implemented in software.

Software safety requirements are derived from a technical risk management process that is closely integrated with the system requirements development process. Software requirement specifications should identify clearly the potential hazards that can result from a software failure in the system as well as any safety requirements to be implemented in software. The consequences of software failure should be evaluated, along with means of mitigating such failures (e.g., hardware mitigation, defensive programming, etc.). From this analysis, it should be possible to identify the most appropriate measures necessary to prevent harm.

The Quality System regulation requires a mechanism for addressing incomplete, ambiguous, or conflicting requirements. (See 21 CFR 820.30(c).) Each requirement (e.g., hardware, software, user, operator interface, and safety) identified in the software requirements specification should be evaluated for accuracy, completeness, consistency, testability, correctness, and clarity. For example, software requirements should be evaluated to verify that:

- There are no internal inconsistencies among requirements;
- All of the performance requirements for the system have been spelled out;
- Fault tolerance, safety, and security requirements are complete and correct;
- Allocation of software functions is accurate and complete;
- Software requirements are appropriate for the system hazards; and
- All requirements are expressed in terms that are measurable or objectively verifiable.

A software requirements traceability analysis should be conducted to trace software requirements to (and from) system requirements and to risk analysis results. In addition to any other analyses and documentation used to verify software requirements, a formal design review is recommended to confirm that requirements are fully specified and appropriate before extensive software design efforts begin. Requirements can be approved and released incrementally, but care should be taken that interactions and interfaces among software (and hardware) requirements are properly reviewed, analyzed, and controlled.

Typical Tasks – Requirements

- Preliminary Risk Analysis
- Traceability Analysis
  - Software Requirements to System Requirements (and vice versa)
  - Software Requirements to Risk Analysis
- Description of User Characteristics
- Listing of Characteristics and Limitations of Primary and Secondary Memory
- Software Requirements Evaluation
- Software User Interface Requirements Analysis
- System Test Plan Generation
- Acceptance Test Plan Generation
- Ambiguity Review or Analysis

5.2.3. Design

In the design process, the software requirements specification is translated into a logical and physical representation of the software to be implemented. The software design specification is a description of what the software should do and how it should do it. Due to complexity of the project or to enable

persons with varying levels of technical responsibilities to clearly understand design information, the design specification may contain both a high level summary of the design and detailed design information. The completed software design specification constrains the programmer/coder to stay within the intent of the agreed upon requirements and design. A complete software design specification will relieve the programmer from the need to make ad hoc design decisions.

The software design needs to address human factors. Use error caused by designs that are either overly complex or contrary to users' intuitive expectations for operation is one of the most persistent and critical problems encountered by FDA. Frequently, the design of the software is a factor in such use errors. Human factors engineering should be woven into the entire design and development process, including the device design requirements, analyses, and tests. Device safety and usability issues should be considered when developing flowcharts, state diagrams, prototyping tools, and test plans. Also, task and function analyses, risk analyses, prototype tests and reviews, and full usability tests should be performed. Participants from the user population should be included when applying these methodologies.

The software design specification should include:

- Software requirements specification, including predetermined criteria for acceptance of the software;
- Software risk analysis;
- Development procedures and coding guidelines (or other programming procedures);
- Systems documentation (e.g., a narrative or a context diagram) that describes the systems context in which the program is intended to function, including the relationship of hardware, software, and the physical environment;
- Hardware to be used;
- Parameters to be measured or recorded;
- Logical structure (including control logic) and logical processing steps (e.g., algorithms);
- Data structures and data flow diagrams;
- Definitions of variables (control and data) and description of where they are used;
- Error, alarm, and warning messages;
- Supporting software (e.g., operating systems, drivers, other application software);
- Communication links (links among internal modules of the software, links with the supporting software, links with the hardware, and links with the user);
- Security measures (both physical and logical security); and
- Any additional constraints not identified in the above elements.

The first four of the elements noted above usually are separate pre-existing documents that are included by reference in the software design specification. Software requirements specification was discussed in the preceding section, as was software risk analysis. Written development procedures serve as a guide to the organization, and written programming procedures serve as a guide to individual programmers. As software cannot be validated without knowledge of the context in which it is intended to function, systems documentation is referenced. If some of the above elements are not included in the software, it

may be helpful to future reviewers and maintainers of the software if that is clearly stated (e.g., There are no error messages in this program).

The activities that occur during software design have several purposes. Software design evaluations are conducted to determine if the design is complete, correct, consistent, unambiguous, feasible, and maintainable. Appropriate consideration of software architecture (e.g., modular structure) during design can reduce the magnitude of future validation efforts when software changes are needed. Software design evaluations may include analyses of control flow, data flow, complexity, timing, sizing, memory allocation, criticality analysis, and many other aspects of the design. A traceability analysis should be conducted to verify that the software design implements all of the software requirements. As a technique for identifying where requirements are not sufficient, the traceability analysis should also verify that all aspects of the design are traceable to software requirements. An analysis of communication links should be conducted to evaluate the proposed design with respect to hardware, user, and related software requirements. The software risk analysis should be re-examined to determine whether any additional hazards have been identified and whether any new hazards have been introduced by the design.

At the end of the software design activity, a Formal Design Review should be conducted to verify that the design is correct, consistent, complete, accurate, and testable, before moving to implement the design. Portions of the design can be approved and released incrementally for implementation; but care should be taken that interactions and communication links among various elements are properly reviewed, analyzed, and controlled.

Most software development models will be iterative. This is likely to result in several versions of both the software requirement specification and the software design specification. All approved versions should be archived and controlled in accordance with established configuration management procedures.

Typical Tasks – Design

- Updated Software Risk Analysis
- Traceability Analysis - Design Specification to Software Requirements (and vice versa)
- Software Design Evaluation
- Design Communication Link Analysis
- Module Test Plan Generation
- Integration Test Plan Generation
- Test Design Generation (module, integration, system, and acceptance)

5.2.4. Construction or Coding

Software may be constructed either by coding (i.e., programming) or by assembling together previously coded software components (e.g., from code libraries, off-the-shelf software, etc.) for use in a new application. Coding is the software activity where the detailed design specification is implemented as source code. Coding is the lowest level of abstraction for the software development process. It is the last stage in decomposition of the software requirements where module specifications are translated into a programming language.

Coding usually involves the use of a high-level programming language, but may also entail the use of assembly language (or microcode) for time-critical operations. The source code may be either compiled or interpreted for use on a target hardware platform. Decisions on the selection of programming languages and software build tools (assemblers, linkers, and compilers) should include consideration of the impact on subsequent quality evaluation tasks (e.g., availability of debugging and testing tools for the chosen language). Some compilers offer optional levels and commands for error checking to assist in debugging the code. Different levels of error checking may be used throughout the coding process, and warnings or other messages from the compiler may or may not be recorded. However, at the end of the coding and debugging process, the most rigorous level of error checking is normally used to document what compilation errors still remain in the software. If the most rigorous level of error checking is not used for final translation of the source code, then justification for use of the less rigorous translation error checking should be documented. Also, for the final compilation, there should be documentation of the compilation process and its outcome, including any warnings or other messages from the compiler and their resolution, or justification for the decision to leave issues unresolved.

Firms frequently adopt specific coding guidelines that establish quality policies and procedures related to the software coding process. Source code should be evaluated to verify its compliance with specified coding guidelines. Such guidelines should include coding conventions regarding clarity, style, complexity management, and commenting. Code comments should provide useful and descriptive information for a module, including expected inputs and outputs, variables referenced, expected data types, and operations to be performed. Source code should also be evaluated to verify its compliance with the corresponding detailed design specification. Modules ready for integration and test should have documentation of compliance with coding guidelines and any other applicable quality policies and procedures.

Source code evaluations are often implemented as code inspections and code walkthroughs. Such static analyses provide a very effective means to detect errors before execution of the code. They allow for examination of each error in isolation and can also help in focusing later dynamic testing of the software. Firms may use manual (desk) checking with appropriate controls to ensure consistency and independence. Source code evaluations should be extended to verification of internal linkages between modules and layers (horizontal and vertical interfaces), and compliance with their design specifications. Documentation of the procedures used and the results of source code evaluations should be maintained as part of design verification.

A source code traceability analysis is an important tool to verify that all code is linked to established specifications and established test procedures. A source code traceability analysis should be conducted and documented to verify that:

- Each element of the software design specification has been implemented in code;
- Modules and functions implemented in code can be traced back to an element in the software design specification and to the risk analysis;
- Tests for modules and functions can be traced back to an element in the software design specification and to the risk analysis; and
- Tests for modules and functions can be traced to source code for the same modules and functions.

Typical Tasks – Construction or Coding

- Traceability Analyses
  - Source Code to Design Specification (and vice versa)
  - Test Cases to Source Code and to Design Specification
- Source Code and Source Code Documentation Evaluation
- Source Code Interface Analysis
- Test Procedure and Test Case Generation (module, integration, system, and acceptance)

5.2.5. Testing by the Software Developer

Software testing entails running software products under known conditions with defined inputs and documented outcomes that can be compared to their predefined expectations. It is a time consuming, difficult, and imperfect activity. As such, it requires early planning in order to be effective and efficient.

Test plans and test cases should be created as early in the software development process as feasible. They should identify the schedules, environments, resources (personnel, tools, etc.), methodologies, cases (inputs, procedures, outputs, expected results), documentation, and reporting criteria. The magnitude of effort to be applied throughout the testing process can be linked to complexity, criticality, reliability, and/or safety issues (e.g., requiring functions or modules that produce critical outcomes to be challenged with intensive testing of their fault tolerance features). Descriptions of categories of software and software testing effort appear in the literature, for example:

- NIST Special Publication 500-235, *Structured Testing: A Testing Methodology Using the Cyclomatic Complexity Metric*;
- NUREG/CR-6293, *Verification and Validation Guidelines for High Integrity Systems*; and
- IEEE Computer Society Press, *Handbook of Software Reliability Engineering*.

Software test plans should identify the particular tasks to be conducted at each stage of development and include justification of the level of effort represented by their corresponding completion criteria.

Software testing has limitations that must be recognized and considered when planning the testing of a particular software product. Except for the simplest of programs, software cannot be exhaustively tested. Generally it is not feasible to test a software product with all possible inputs, nor is it possible to test all possible data processing paths that can occur during program execution. There is no one type of testing or testing methodology that can ensure a particular software product has been thoroughly tested. Testing of all program functionality does not mean all of the program has been tested. Testing of all of a program's code does not mean all necessary functionality is present in the program. Testing of all program functionality and all program code does not mean the program is 100% correct! Software testing that finds no errors should not be interpreted to mean that errors do not exist in the software product; it may mean the testing was superficial.

An essential element of a software test case is the expected result. It is the key detail that permits objective evaluation of the actual test result. This necessary testing information is obtained from the corresponding, predefined definition or specification. A software specification document must identify what, when, how, why, etc., is to be achieved with an engineering (i.e., measurable or objectively verifiable) level of detail in order for it to be confirmed through testing. The real effort of effective software testing lies in the definition of what is to be tested rather than in the performance of the test.

A software testing process should be based on principles that foster effective examinations of a software product. Applicable software testing tenets include:

- The expected test outcome is predefined;
- A good test case has a high probability of exposing an error;
- A successful test is one that finds an error;
- There is independence from coding;
- Both application (user) and software (programming) expertise are employed;
- Testers use different tools from coders;
- Examining only the usual case is insufficient;
- Test documentation permits its reuse and an independent confirmation of the pass/fail status of a test outcome during subsequent review.

Once the prerequisite tasks (e.g., code inspection) have been successfully completed, software testing begins. It starts with unit level testing and concludes with system level testing. There may be a distinct integration level of testing. A software product should be challenged with test cases based on its internal structure and with test cases based on its external specification. These tests should provide a thorough and rigorous examination of the software product's compliance with its functional, performance, and interface definitions and requirements.

Code-based testing is also known as structural testing or "white-box" testing. It identifies test cases based on knowledge obtained from the source code, detailed design specification, and other development documents. These test cases challenge the control decisions made by the program; and the program's data structures including configuration tables. Structural testing can identify "dead" code

that is never executed when the program is run. Structural testing is accomplished primarily with unit (module) level testing, but can be extended to other levels of software testing.

The level of structural testing can be evaluated using metrics that are designed to show what percentage of the software structure has been evaluated during structural testing. These metrics are typically referred to as "coverage" and are a measure of completeness with respect to test selection criteria. The amount of structural coverage should be commensurate with the level of risk posed by the software. Use of the term "coverage" usually means 100% coverage. For example, if a testing program has achieved "statement coverage," it means that 100% of the statements in the software have been executed at least once. Common structural coverage metrics include:

- **Statement Coverage** – This criteria requires sufficient test cases for each program statement to be executed at least once; however, its achievement is insufficient to provide confidence in a software product's behavior.

- **Decision (Branch) Coverage** – This criteria requires sufficient test cases for each program decision or branch to be executed so that each possible outcome occurs at least once. It is considered to be a minimum level of coverage for most software products, but decision coverage alone is insufficient for high-integrity applications.

- **Condition Coverage** – This criteria requires sufficient test cases for each condition in a program decision to take on all possible outcomes at least once. It differs from branch coverage only when multiple conditions must be evaluated to reach a decision.

- **Multi-Condition Coverage** – This criteria requires sufficient test cases to exercise all possible combinations of conditions in a program decision.

- **Loop Coverage** – This criteria requires sufficient test cases for all program loops to be executed for zero, one, two, and many iterations covering initialization, typical running and termination (boundary) conditions.

- **Path Coverage** – This criteria requires sufficient test cases for each feasible path, basis path, etc., from start to exit of a defined program segment, to be executed at least once. Because of the very large number of possible paths through a software program, path coverage is generally not achievable. The amount of path coverage is normally established based on the risk or criticality of the software under test.

- **Data Flow Coverage** – This criteria requires sufficient test cases for each feasible data flow to be executed at least once. A number of data flow testing strategies are available.

Definition-based or specification-based testing is also known as functional testing or "black-box" testing. It identifies test cases based on the definition of what the software product (whether it be a unit (module) or a complete program) is intended to do. These test cases challenge the intended use or functionality of a program, and the program's internal and external interfaces. Functional testing can be applied at all levels of software testing, from unit to system level testing.

The following types of functional software testing involve generally increasing levels of effort:

- **Normal Case** – Testing with usual inputs is necessary. However, testing a software product only with expected, valid inputs does not thoroughly test that software product. By itself, normal case testing cannot provide sufficient confidence in the dependability of the software product.

- **Output Forcing** – Choosing test inputs to ensure that selected (or all) software outputs are generated by testing.

- **Robustness** – Software testing should demonstrate that a software product behaves correctly when given unexpected, invalid inputs. Methods for identifying a sufficient set of such test cases include Equivalence Class Partitioning, Boundary Value Analysis, and Special Case Identification (Error Guessing). While important and necessary, these techniques do not ensure that all of the most appropriate challenges to a software product have been identified for testing.

- **Combinations of Inputs** – The functional testing methods identified above all emphasize individual or single test inputs. Most software products operate with multiple inputs under their conditions of use. Thorough software product testing should consider the combinations of inputs a software unit or system may encounter during operation. Error guessing can be extended to identify combinations of inputs, but it is an ad hoc technique. Cause-effect graphing is one functional software testing technique that systematically identifies combinations of inputs to a software product for inclusion in test cases.

Functional and structural software test case identification techniques provide specific inputs for testing, rather than random test inputs. One weakness of these techniques is the difficulty in linking structural and functional test completion criteria to a software product's reliability. Advanced software testing methods, such as statistical testing, can be employed to provide further assurance that a software product is dependable. Statistical testing uses randomly generated test data from defined distributions based on an operational profile (e.g., expected use, hazardous use, or malicious use of the software product). Large amounts of test data are generated and can be targeted to cover particular areas or concerns, providing an increased possibility of identifying individual and multiple rare operating conditions that were not anticipated by either the software product's designers or its testers. Statistical testing also provides high structural coverage. It does require a stable software product. Thus, structural and functional testing are prerequisites for statistical testing of a software product.

Another aspect of software testing is the testing of software changes. Changes occur frequently during software development. These changes are the result of 1) debugging that finds an error and it is corrected, 2) new or changed requirements ("requirements creep"), and 3) modified designs as more effective or efficient implementations are found. Once a software product has been baselined (approved), any change to that product should have its own “mini life cycle,” including testing. Testing of a changed software product requires additional effort. Not only should it demonstrate that the change was implemented correctly, testing should also demonstrate that the change did not adversely impact other parts of the software product. Regression analysis and testing are employed to provide

assurance that a change has not created problems elsewhere in the software product. Regression analysis is the determination of the impact of a change based on review of the relevant documentation (e.g., software requirements specification, software design specification, source code, test plans, test cases, test scripts, etc.) in order to identify the necessary regression tests to be run. Regression testing is the rerunning of test cases that a program has previously executed correctly and comparing the current result to the previous result in order to detect unintended effects of a software change. Regression analysis and regression testing should also be employed when using integration methods to build a software product to ensure that newly integrated modules do not adversely impact the operation of previously integrated modules.

In order to provide a thorough and rigorous examination of a software product, development testing is typically organized into levels. As an example, a software product's testing can be organized into unit, integration, and system levels of testing.

1) Unit (module or component) level testing focuses on the early examination of sub-program functionality and ensures that functionality not visible at the system level is examined by testing. Unit testing ensures that quality software units are furnished for integration into the finished software product.

2) Integration level testing focuses on the transfer of data and control across a program's internal and external interfaces. External interfaces are those with other software (including operating system software), system hardware, and the users and can be described as communications links.

3) System level testing demonstrates that all specified functionality exists and that the software product is trustworthy. This testing verifies the as-built program's functionality and performance with respect to the requirements for the software product as exhibited on the specified operating platform(s). System level software testing addresses functional concerns and the following elements of a device's software that are related to the intended use(s):

    - Performance issues (e.g., response times, reliability measurements);
    - Responses to stress conditions, e.g., behavior under maximum load, continuous use;
    - Operation of internal and external security features;
    - Effectiveness of recovery procedures, including disaster recovery;
    - Usability;
    - Compatibility with other software products;
    - Behavior in each of the defined hardware configurations; and
    - Accuracy of documentation.

Control measures (e.g., a traceability analysis) should be used to ensure that the intended coverage is achieved.

System level testing also exhibits the software product's behavior in the intended operating environment. The location of such testing is dependent upon the software developer's ability to produce the target operating environment(s). Depending upon the circumstances, simulation and/or testing at (potential) customer locations may be utilized. Test plans should identify the controls needed to ensure that the

intended coverage is achieved and that proper documentation is prepared when planned system level testing is conducted at sites not directly controlled by the software developer. Also, for a software product that is a medical device or a component of a medical device that is to be used on humans prior to FDA clearance, testing involving human subjects may require an Investigational Device Exemption (IDE) or Institutional Review Board (IRB) approval.

Test procedures, test data, and test results should be documented in a manner permitting objective pass/fail decisions to be reached. They should also be suitable for review and objective decision making subsequent to running the test, and they should be suitable for use in any subsequent regression testing. Errors detected during testing should be logged, classified, reviewed, and resolved prior to release of the software. Software error data that is collected and analyzed during a development life cycle may be used to determine the suitability of the software product for release for commercial distribution. Test reports should comply with the requirements of the corresponding test plans.

Software products that perform useful functions in medical devices or their production are often complex. Software testing tools are frequently used to ensure consistency, thoroughness, and efficiency in the testing of such software products and to fulfill the requirements of the planned testing activities. These tools may include supporting software built in-house to facilitate unit (module) testing and subsequent integration testing (e.g., drivers and stubs) as well as commercial software testing tools. Such tools should have a degree of quality no less than the software product they are used to develop. Appropriate documentation providing evidence of the validation of these software tools for their intended use should be maintained (see section 6 of this guidance).

Typical Tasks – Testing by the Software Developer

- Test Planning
- Structural Test Case Identification
- Functional Test Case Identification
- Traceability Analysis - Testing
  - Unit (Module) Tests to Detailed Design
  - Integration Tests to High Level Design
  - System Tests to Software Requirements
- Unit (Module) Test Execution
- Integration Test Execution
- Functional Test Execution
- System Test Execution
- Acceptance Test Execution
- Test Results Evaluation
- Error Evaluation/Resolution
- Final Test Report

5.2.6. User Site Testing

Testing at the user site is an essential part of software validation. The Quality System regulation requires installation and inspection procedures (including testing where appropriate) as well as documentation of inspection and testing to demonstrate proper installation. (See 21 CFR §820.170.) Likewise, manufacturing equipment must meet specified requirements, and automated systems must be validated for their intended use. (See 21 CFR §820.70(g) and 21 CFR §820.70(i) respectively.)

Terminology regarding user site testing can be confusing. Terms such as beta test, site validation, user acceptance test, installation verification, and installation testing have all been used to describe user site testing. For purposes of this guidance, the term "user site testing" encompasses all of these and any other testing that takes place outside of the developer's controlled environment. This testing should take place at a user's site with the actual hardware and software that will be part of the installed system configuration. The testing is accomplished through either actual or simulated use of the software being tested within the context in which it is intended to function.

Guidance contained here is general in nature and is applicable to any user site testing. However, in some areas (e.g., blood establishment systems) there may be specific site validation issues that need to be considered in the planning of user site testing. Test planners should check with the FDA Center(s) with the corresponding product jurisdiction to determine whether there are any additional regulatory requirements for user site testing.

User site testing should follow a pre-defined written plan with a formal summary of testing and a record of formal acceptance. Documented evidence of all testing procedures, test input data, and test results should be retained.

There should be evidence that hardware and software are installed and configured as specified. Measures should ensure that all system components are exercised during the testing and that the versions of these components are those specified. The testing plan should specify testing throughout the full range of operating conditions and should specify continuation for a sufficient time to allow the system to encounter a wide spectrum of conditions and events in an effort to detect any latent faults that are not apparent during more normal activities.

Some of the evaluations that have been performed earlier by the software developer at the developer's site should be repeated at the site of actual use. These may include tests for a high volume of data, heavy loads or stresses, security, fault testing (avoidance, detection, tolerance, and recovery), error messages, and implementation of safety requirements. The developer may be able to furnish the user with some of the test data sets to be used for this purpose.

In addition to an evaluation of the system's ability to properly perform its intended functions, there should be an evaluation of the ability of the users of the system to understand and correctly interface with it. Operators should be able to perform the intended functions and respond in an appropriate and timely manner to all alarms, warnings, and error messages.

During user site testing, records should be maintained of both proper system performance and any system failures that are encountered. The revision of the system to compensate for faults detected during this user site testing should follow the same procedures and controls as for any other software change.

The developers of the software may or may not be involved in the user site testing. If the developers are involved, they may seamlessly carry over to the user's site the last portions of design-level systems testing. If the developers are not involved, it is all the more important that the user have persons who understand the importance of careful test planning, the definition of expected test results, and the recording of all test outputs.

Typical Tasks – User Site Testing

- Acceptance Test Execution
- Test Results Evaluation
- Error Evaluation/Resolution
- Final Test Report

5.2.7. Maintenance and Software Changes

As applied to software, the term maintenance does not mean the same as when applied to hardware. The operational maintenance of hardware and software are different because their failure/error mechanisms are different. Hardware maintenance typically includes preventive hardware maintenance actions, component replacement, and corrective changes. Software maintenance includes corrective, perfective, and adaptive maintenance but does not include preventive maintenance actions or software component replacement.

Changes made to correct errors and faults in the software are corrective maintenance. Changes made to the software to improve the performance, maintainability, or other attributes of the software system are perfective maintenance. Software changes to make the software system usable in a changed environment are adaptive maintenance.

When changes are made to a software system, either during initial development or during post release maintenance, sufficient regression analysis and testing should be conducted to demonstrate that portions of the software not involved in the change were not adversely impacted. This is in addition to testing that evaluates the correctness of the implemented change(s).

The specific validation effort necessary for each software change is determined by the type of change, the development products affected, and the impact of those products on the operation of the software. Careful and complete documentation of the design structure and interrelationships of various modules, interfaces, etc., can limit the validation effort needed when a change is made. The level of effort needed

to fully validate a change is also dependent upon the degree to which validation of the original software was documented and archived. For example, test documentation, test cases, and results of previous verification and validation testing need to be archived if they are to be available for performing subsequent regression testing. Failure to archive this information for later use can significantly increase the level of effort and expense of revalidating the software after a change is made.

In addition to software verification and validation tasks that are part of the standard software development process, the following additional maintenance tasks should be addressed:

- **Software Validation Plan Revision** - For software that was previously validated, the existing software validation plan should be revised to support the validation of the revised software. If no previous software validation plan exists, such a plan should be established to support the validation of the revised software.

- **Anomaly Evaluation** – Software organizations frequently maintain documentation, such as software problem reports that describe software anomalies discovered and the specific corrective action taken to fix each anomaly. Too often, however, mistakes are repeated because software developers do not take the next step to determine the root causes of problems and make the process and procedural changes needed to avoid recurrence of the problem. Software anomalies should be evaluated in terms of their severity and their effects on system operation and safety, but they should also be treated as symptoms of process deficiencies in the quality system. A root cause analysis of anomalies can identify specific quality system deficiencies. Where trends are identified (e.g., recurrence of similar software anomalies), appropriate corrective and preventive actions must be implemented and documented to avoid further recurrence of similar quality problems. (See 21 CFR 820.100.)

- **Problem Identification and Resolution Tracking** - All problems discovered during maintenance of the software should be documented. The resolution of each problem should be tracked to ensure it is fixed, for historical reference, and for trending.

- **Proposed Change Assessment** - All proposed modifications, enhancements, or additions should be assessed to determine the effect each change would have on the system. This information should determine the extent to which verification and/or validation tasks need to be iterated.

- **Task Iteration** - For approved software changes, all necessary verification and validation tasks should be performed to ensure that planned changes are implemented correctly, all documentation is complete and up to date, and no unacceptable changes have occurred in software performance.

- **Documentation Updating** – Documentation should be carefully reviewed to determine which documents have been impacted by a change. All approved documents (e.g., specifications, test procedures, user manuals, etc.) that have been affected should be updated in accordance with configuration management procedures. Specifications should be updated before any maintenance and software changes are made.

SECTION 6. VALIDATION OF AUTOMATED PROCESS EQUIPMENT AND QUALITY SYSTEM SOFTWARE

The Quality System regulation requires that "when computers or automated data processing systems are used as part of production or the quality system, the [device] manufacturer shall validate computer software for its intended use according to an established protocol." (See 21 CFR §820.70(i)). This has been a regulatory requirement of FDA's medical device Good Manufacturing Practice (GMP) regulations since 1978.

In addition to the above validation requirement, computer systems that implement part of a device manufacturer's production processes or quality system (or that are used to create and maintain records required by any other FDA regulation) are subject to the Electronic Records; Electronic Signatures regulation. (See 21 CFR Part 11.) This regulation establishes additional security, data integrity, and validation requirements when records are created or maintained electronically. These additional Part 11 requirements should be carefully considered and included in system requirements and software requirements for any automated record `keeping systems. System validation and software validation should demonstrate that all Part 11 requirements have been met.

Computers and automated equipment are used extensively throughout all aspects of medical device design, laboratory testing and analysis, product inspection and acceptance, production and process control, environmental controls, packaging, labeling, traceability, document control, complaint management, and many other aspects of the quality system. Increasingly, automated plant floor operations can involve extensive use of embedded systems in:

- programmable logic controllers;
- digital function controllers;
- statistical process control;
- supervisory control and data acquisition;
- robotics;
- human-machine interfaces;
- input/output devices; and
- computer operating systems.

Software tools are frequently used to design, build, and test the software that goes into an automated medical device. Many other commercial software applications, such as word processors, spreadsheets, databases, and flowcharting software are used to implement the quality system. All of these applications are subject to the requirement for software validation, but the validation approach used for each application can vary widely.

Whether production or quality system software is developed in-house by the device manufacturer, developed by a contractor, or purchased off-the-shelf, it should be developed using the basic principles

outlined elsewhere in this guidance. The device manufacturer has latitude and flexibility in defining how validation of that software will be accomplished, but validation should be a key consideration in deciding how and by whom the software will be developed or from whom it will be purchased. The software developer defines a life cycle model. Validation is typically supported by:

- verifications of the outputs from each stage of that software development life cycle; and
- checking for proper operation of the finished software in the device manufacturer's intended use environment.

6.1. HOW MUCH VALIDATION EVIDENCE IS NEEDED?

The level of validation effort should be commensurate with the risk posed by the automated operation. In addition to risk other factors, such as the complexity of the process software and the degree to which the device manufacturer is dependent upon that automated process to produce a safe and effective device, determine the nature and extent of testing needed as part of the validation effort. Documented requirements and risk analysis of the automated process help to define the scope of the evidence needed to show that the software is validated for its intended use. For example, an automated milling machine may require very little testing if the device manufacturer can show that the output of the operation is subsequently fully verified against the specification before release. On the other hand, extensive testing may be needed for:

- a plant-wide electronic record and electronic signature system;
- an automated controller for a sterilization cycle; or
- automated test equipment used for inspection and acceptance of finished circuit boards in a life-sustaining / life-supporting device.

Numerous commercial software applications may be used as part of the quality system (e.g., a spreadsheet or statistical package used for quality system calculations, a graphics package used for trend analysis, or a commercial database used for recording device history records or for complaint management). The extent of validation evidence needed for such software depends on the device manufacturer's documented intended use of that software. For example, a device manufacturer who chooses not to use all the vendor-supplied capabilities of the software only needs to validate those functions that will be used and for which the device manufacturer is dependent upon the software results as part of production or the quality system. However, high risk applications should not be running in the same operating environment with non-validated software functions, even if those software functions are not used. Risk mitigation techniques such as memory partitioning or other approaches to resource protection may need to be considered when high risk applications and lower risk applications are to be used in the same operating environment. When software is upgraded or any changes are made to the software, the device manufacturer should consider how those changes may impact the "used portions" of the software and must reconfirm the validation of those portions of the software that are used. (See 21 CFR §820.70(i).)

6.2. DEFINED USER REQUIREMENTS

A very important key to software validation is a documented user requirements specification that defines:

- the "intended use" of the software or automated equipment; and
- the extent to which the device manufacturer is dependent upon that software or equipment for production of a quality medical device.

The device manufacturer (user) needs to define the expected operating environment including any required hardware and software configurations, software versions, utilities, etc. The user also needs to:

- document requirements for system performance, quality, error handling, startup, shutdown, security, etc.;
- identify any safety related functions or features, such as sensors, alarms, interlocks, logical processing steps, or command sequences; and
- define objective criteria for determining acceptable performance.

The validation must be conducted in accordance with a documented protocol, and the validation results must also be documented. (See 21 CFR §820.70(i).) Test cases should be documented that will exercise the system to challenge its performance against the pre-determined criteria, especially for its most critical parameters. Test cases should address error and alarm conditions, startup, shutdown, all applicable user functions and operator controls, potential operator errors, maximum and minimum ranges of allowed values, and stress conditions applicable to the intended use of the equipment. The test cases should be executed and the results should be recorded and evaluated to determine whether the results support a conclusion that the software is validated for its intended use.

A device manufacturer may conduct a validation using their own personnel or may depend on a third party such as the equipment/software vendor or a consultant. In any case, the device manufacturer retains the ultimate responsibility for ensuring that the production and quality system software:

- is validated according to a written procedure for the particular intended use; and
- will perform as intended in the chosen application.

The device manufacturer should have documentation including:

- defined user requirements;
- validation protocol used;
- acceptance criteria;
- test cases and results; and
- a validation summary

that objectively confirms that the software is validated for its intended use.

6.3. VALIDATION OF OFF-THE-SHELF SOFTWARE AND AUTOMATED EQUIPMENT

Most of the automated equipment and systems used by device manufacturers are supplied by third-party vendors and are purchased off-the-shelf (OTS). The device manufacturer is responsible for ensuring that the product development methodologies used by the OTS software developer are appropriate and sufficient for the device manufacturer's intended use of that OTS software. For OTS software and equipment, the device manufacturer may or may not have access to the vendor's software validation documentation. If the vendor can provide information about their system requirements, software requirements, validation process, and the results of their validation, the medical device manufacturer can use that information as a beginning point for their required validation documentation. The vendor's life cycle documentation, such as testing protocols and results, source code, design specification, and requirements specification, can be useful in establishing that the software has been validated. However, such documentation is frequently not available from commercial equipment vendors, or the vendor may refuse to share their proprietary information.

Where possible and depending upon the device risk involved, the device manufacturer should consider auditing the vendor's design and development methodologies used in the construction of the OTS software and should assess the development and validation documentation generated for the OTS software. Such audits can be conducted by the device manufacturer or by a qualified third party. The audit should demonstrate that the vendor's procedures for and results of the verification and validation activities performed the OTS software are appropriate and sufficient for the safety and effectiveness requirements of the medical device to be produced using that software.

Some vendors who are not accustomed to operating in a regulated environment may not have a documented life cycle process that can support the device manufacturer's validation requirement. Other vendors may not permit an audit. Where necessary validation information is not available from the vendor, the device manufacturer will need to perform sufficient system level "black box" testing to establish that the software meets their "user needs and intended uses." For many applications black box testing alone is not sufficient. Depending upon the risk of the device produced, the role of the OTS software in the process, the ability to audit the vendor, and the sufficiency of vendor-supplied information, the use of OTS software or equipment may or may not be appropriate, especially if there are suitable alternatives available. The device manufacturer should also consider the implications (if any) for continued maintenance and support of the OTS software should the vendor terminate their support.

For some off-the-shelf software development tools, such as software compilers, linkers, editors, and operating systems, exhaustive black-box testing by the device manufacturer may be impractical. Without such testing – a key element of the validation effort – it may not be possible to validate these software tools. However, their proper operation may be satisfactorily inferred by other means. For example, compilers are frequently certified by independent third-party testing, and commercial software products may have "bug lists", system requirements and other operational information available from the vendor that can be compared to the device manufacturer's intended use to help focus the "black-box" testing effort. Off-the-shelf operating systems need not be validated as a separate program. However, system-level validation testing of the application software should address all the operating system services used, including maximum loading conditions, file operations, handling of system error

conditions, and memory constraints that may be applicable to the intended use of the application program.

For more detailed information, see the production and process software references in Appendix A.

APPENDIX A - REFERENCES

Food and Drug Administration References

Design Control Guidance for Medical Device Manufacturers, Center for Devices and Radiological Health, Food and Drug Administration, March 1997.

Do It by Design, An Introduction to Human Factors in Medical Devices, Center for Devices and Radiological Health, Food and Drug Administration, March 1997.

Electronic Records; Electronic Signatures Final Rule, 62 Federal Register 13430 (March 20, 1997).

Glossary of Computerized System and Software Development Terminology, Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, Food and Drug Administration, August 1995.

Guidance for the Content of Pre-market Submissions for Software Contained in Medical Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, May 1998.

Guidance for Industry, FDA Reviewers and Compliance on Off-the-Shelf Software Use in Medical Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, September 1999.

Guideline on General Principles of Process Validation, Center for Drugs and Biologics, & Center For Devices and Radiological Health, Food and Drug Administration, May 1987.

Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation, 61 Federal Register 52602 (October 7, 1996).

Reviewer Guidance for a Pre-Market Notification Submission for Blood Establishment Computer Software, Center for Biologics Evaluation and Research, Food and Drug Administration, January 1997

Student Manual 1, Course INV545, Computer System Validation, Division of Human Resource Development, Office of Regulatory Affairs, Food and Drug Administration, 1997.

Technical Report, Software Development Activities, Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, Food and Drug Administration, July 1987.

Other Government References

W. Richards Adrion, Martha A. Branstad, John C. Cherniavsky. *NBS Special Publication 500-75, Validation, Verification, and Testing of Computer Software,* Center for Programming Science and Technology, Institute for Computer Sciences and Technology, National Bureau of Standards, U.S. Department of Commerce, February 1981.

Martha A. Branstad, John C Cherniavsky, W. Richards Adrion, *NBS Special Publication 500-56, Validation, Verification, and Testing for the Individual Programmer*, Center for Programming Science and Technology, Institute for Computer Sciences and Technology, National Bureau of Standards, U.S. Department of Commerce, February 1980.

J.L. Bryant, N.P. Wilburn, *Handbook of Software Quality Assurance Techniques Applicable to the Nuclear Industry*, NUREG/CR-4640, U.S. Nuclear Regulatory Commission, 1987.

H. Hecht, et.al., *Verification and Validation Guidelines for High Integrity Systems.* NUREG/CR-6293. Prepared for U.S. Nuclear Regulatory Commission, 1995.

H. Hecht, et.al., *Review Guidelines on Software Languages for Use in Nuclear Power Plant Safety Systems, Final Report*. NUREG/CR-6463. Prepared for U.S. Nuclear Regulatory Commission, 1996.

J.D. Lawrence, W.L. Persons, *Survey of Industry Methods for Producing Highly Reliable Software*, NUREG/CR-6278, U.S. Nuclear Regulatory Commission, 1994.

J.D. Lawrence, G.G. Preckshot, *Design Factors for Safety-Critical Software,* NUREG/CR-6294, U.S. Nuclear Regulatory Commission, 1994.

Patricia B. Powell, Editor. *NBS Special Publication 500-98, Planning for Software Validation, Verification, and Testing,* Center for Programming Science and Technology, Institute for Computer Sciences and Technology, National Bureau of Standards, U.S. Department of Commerce, November 1982.

Patricia B. Powell, Editor. *NBS Special Publication 500-93, Software Validation, Verification, and Testing Technique and Tool Reference Guide*, Center for Programming Science and Technology, Institute for Computer Sciences and Technology, National Bureau of Standards, U.S. Department of Commerce, September 1982.

Delores R. Wallace, Roger U. Fujii, *NIST Special Publication 500-165, Software Verification and Validation: Its Role in Computer Assurance and Its Relationship with Software Project Management Standards*, National Computer Systems Laboratory, National Institute of Standards and Technology, U.S. Department of Commerce, September 1995.

Delores R. Wallace, Laura M. Ippolito, D. Richard Kuhn, *NIST Special Publication 500-204, High Integrity Software, Standards and Guidelines*, Computer Systems Laboratory, National Institute of

Standards and Technology, U.S. Department of Commerce, September 1992.

Delores R. Wallace, et.al. *NIST Special Publication 500-234, Reference Information for the Software Verification and Validation Process*. Computer Systems Laboratory, National Institute of Standards and Technology, U.S. Department of Commerce, March 1996.

Delores R. Wallace, Editor. *NIST Special Publication 500-235, Structured Testing: A Testing Methodology Using the Cyclomatic Complexity Metric*. Computer Systems Laboratory, National Institute of Standards and Technology, U.S. Department of Commerce, August 1996.

International and National Consensus Standards

ANSI / ANS-10.4-1987, *Guidelines for the Verification and Validation of Scientific and Engineering Computer Programs for the Nuclear Industry*, American National Standards Institute, 1987.

ANSI / ASQC Standard D1160-1995, *Formal Design Reviews,* American Society for Quality Control, 1995.

ANSI / UL 1998:1998, *Standard for Safety for Software in Programmable Components*, Underwriters Laboratories, Inc., 1998.

AS 3563.1-1991, *Software Quality Management System, Part 1: Requirements.* Published by Standards Australia [Standards Association of Australia], 1 The Crescent, Homebush, NSW 2140.

AS 3563.2-1991, *Software Quality Management System, Part 2: Implementation Guide*. Published by Standards Australia [Standards Association of Australia], 1 The Crescent, Homebush, NSW 2140.

IEC 60601-1-4:1996, *Medical electrical equipment, Part 1: General requirements for safety, 4. Collateral Standard: Programmable electrical medical systems.* International Electrotechnical Commission, 1996.

IEC 61506:1997, *Industrial process measurement and control – Documentation of application software*. International Electrotechnical Commission, 1997.

IEC 61508:1998, *Functional safety of electrical/electronic/programmable electronic safety-related systems*. International Electrotechnical Commission, 1998.

IEEE Std 1012-1986, *Software Verification and Validation Plans*, Institute for Electrical and Electronics Engineers, 1986.

IEEE Standards Collection, Software Engineering, Institute of Electrical and Electronics Engineers, Inc., 1994. ISBN 1-55937-442-X.

ISO 8402:1994, *Quality management and quality assurance – Vocabulary*. International Organization for Standardization, 1994.

ISO 9000-3:1997, *Quality management and quality assurance standards - Part 3: Guidelines for the application of ISO 9001:1994 to the development, supply, installation and maintenance of computer software*. International Organization for Standardization, 1997.

ISO 9001:1994, *Quality systems – Model for quality assurance in design, development, production, installation, and servicing*. International Organization for Standardization, 1994.

ISO 13485:1996, *Quality systems – Medical devices – Particular requirements for the application of ISO 9001*. International Organization for Standardization, 1996.

ISO/IEC 12119:1994, *Information technology – Software packages – Quality requirements and testing*, Joint Technical Committee ISO/IEC JTC 1, International Organization for Standardization and International Electrotechnical Commission, 1994.

ISO/IEC 12207:1995, *Information technology – Software life cycle processes*, Joint Technical Committee ISO/IEC JTC 1, Subcommittee SC 7, International Organization for Standardization and International Electrotechnical Commission, 1995.

ISO/IEC 14598:1999, *Information technology – Software product evaluation*, Joint Technical Committee ISO/IEC JTC 1, Subcommittee SC 7, International Organization for Standardization and International Electrotechnical Commission, 1999.

ISO 14971-1:1998, *Medical Devices – Risk Management – Part 1: Application of Risk Analysis.* International Organization for Standardization, 1998.

Software Considerations in Airborne Systems and Equipment Certification. Special Committee 167 of RTCA. RTCA Inc., Washington, D.C. Tel: 202-833-9339. Document No. RTCA/DO-178B, December 1992.

Production Process Software References

The Application of the Principles of GLP to Computerized Systems, Environmental Monograph #116, Organization for Economic Cooperation and Development (OECD), 1995.

George J. Grigonis, Jr., Edward J. Subak, Jr., and Michael Wyrick, "Validation Key Practices for Computer Systems Used in Regulated Operations," *Pharmaceutical Technology*, June 1997.

Guide to Inspection of Computerized Systems in Drug Processing, Reference Materials and

Training Aids for Investigators, Division of Drug Quality Compliance, Associate Director for Compliance, Office of Drugs, National Center for Drugs and Biologics, & Division of Field Investigations, Associate Director for Field Support, Executive Director of Regional Operations, Food and Drug Administration, February 1983.

Daniel P. Olivier, "Validating Process Software", *FDA Investigator Course: Medical Device Process Validation*, Food and Drug Administration.

GAMP Guide For Validation of Automated Systems in Pharmaceutical Manufacture,Version V3.0, Good Automated Manufacturing Practice (GAMP) Forum, March 1998:

Volume 1, Part 1: User Guide
Part 2: Supplier Guide
Volume 2: Best Practice for User and Suppliers.

Technical Report No. 18, Validation of Computer-Related Systems. PDA Committee on Validation of Computer-Related Systems. PDA Journal of Pharmaceutical Science and Technology, Volume 49, Number 1, January-February 1995 Supplement.

Validation Compliance Annual 1995, International Validation Forum, Inc.

General Software Quality References

Boris Beizer, *Black Box Testing, Techniques for Functional Testing of Software and Systems*, John Wiley & Sons, 1995. ISBN 0-471-12094-4.

Boris Beizer, *Software System Testing and Quality Assurance*, International Thomson Computer Press, 1996. ISBN 1-85032-821-8.

Boris Beizer, *Software Testing Techniques*, Second Edition, Van Nostrand Reinhold, 1990. ISBN 0-442-20672-0.

Richard Bender, *Writing Testable Requirements, Version 1.0*, Bender & Associates, Inc., Larkspur, CA 94777, 1996.

Frederick P. Brooks, Jr., *The Mythical Man-Month, Essays on Software Engineering*, Addison-Wesley Longman, Anniversary Edition, 1995. ISBN 0-201-83595-9.

Silvana Castano, et.al., *Database Security*, ACM Press, Addison-Wesley Publishing Company, 1995. ISBN 0-201-59375-0.

Computerized Data Systems for Nonclinical Safety Assessment, Current Concepts and Quality Assurance, Drug Information Association, Maple Glen, PA, September 1988.

M. S. Deutsch, *Software Verification and Validation, Realistic Project Approaches*, Prentice Hall, 1982.

Robert H. Dunn and Richard S. Ullman, *TQM for Computer Software*, Second Edition, McGraw-Hill, Inc., 1994. ISBN 0-07-018314-7.

Elfriede Dustin, Jeff Rashka, and John Paul, *Automated Software Testing – Introduction, Management and Performance*, Addison Wesley Longman, Inc., 1999. ISBN 0-201-43287-0.

Robert G. Ebenau and Susan H. Strauss, *Software Inspection Process*, McGraw-Hill, 1994. ISBN 0-07-062166-7.

Richard E. Fairley, *Software Engineering Concepts*, McGraw-Hill Publishing Company, 1985. ISBN 0-07-019902-7.

Michael A. Friedman and Jeffrey M. Voas, *Software Assessment - Reliability, Safety, Testability*, Wiley-Interscience, John Wiley & Sons Inc., 1995. ISBN 0-471-01009-X.

Tom Gilb, Dorothy Graham, *Software Inspection*, Addison-Wesley Publishing Company, 1993. ISBN 0-201-63181-4.

Robert B. Grady, *Practical Software Metrics for Project Management and Process Improvement*, PTR Prentice-Hall Inc., 1992. ISBN 0-13-720384-5.

Les Hatton, *Safer C: Developing Software for High-integrity and Safety-critical Systems*, McGraw-Hill Book Company, 1994. ISBN 0-07-707640-0.

Janis V. Halvorsen, *A Software Requirements Specification Document Model for the Medical Device Industry*, Proceedings IEEE SOUTHEASTCON '93, Banking on Technology, April 4th -7th, 1993, Charlotte, North Carolina.

Debra S. Herrmann, *Software Safety and Reliability: Techniques, Approaches and Standards of Key Industrial Sectors*, IEEE Computer Society, 1999. ISBN 0-7695-0299-7.

Bill Hetzel, *The Complete Guide to Software Testing*, Second Edition, A Wiley-QED Publication, John Wiley & Sons, Inc., 1988. ISBN 0-471-56567-9.

Watts S. Humphrey, *A Discipline for Software Engineering*. Addison-Wesley Longman, 1995. ISBN 0-201-54610-8.

Watts S. Humphrey, *Managing the Software Process*, Addison-Wesley Publishing Company, 1989. ISBN 0-201-18095-2.

Capers Jones, *Software Quality, Analysis and Guidelines for Success*, International Thomson Computer Press, 1997. ISBN 1-85032-867-6.

J.M. Juran, Frank M. Gryna, *Quality Planning and Analysis*, Third Edition, , McGraw-Hill, 1993. ISBN 0-07-033183-9.

Stephen H. Kan, *Metrics and Models in Software Quality Engineering*, Addison-Wesley Publishing Company, 1995. ISBN 0-201-63339-6.

Cem Kaner, Jack Falk, Hung Quoc Nguyen, *Testing Computer Software*, Second Edition, Vsn Nostrand Reinhold, 1993. ISBN 0-442-01361-2.

Craig Kaplan, Ralph Clark, Victor Tang, *Secrets of Software Quality, 40 Innovations from IBM*, McGraw-Hill, 1995. ISBN 0-07-911795-3.

Edward Kit, *Software Testing in the Real World*, Addison-Wesley Longman, 1995. ISBN 0-201-87756-2.

Alan Kusinitz, "Software Validation", *Current Issues in Medical Device Quality Systems*, Association for the Advancement of Medical Instrumentation, 1997. ISBN 1-57020-075-0.

Nancy G. Leveson, *Safeware, System Safety and Computers*, Addison-Wesley Publishing Company, 1995. ISBN 0-201-11972-2.

Michael R. Lyu, Editor, *Handbook of Software Reliability Engineering*, IEEE Computer Society Press, McGraw-Hill, 1996. ISBN 0-07-039400-8.

Steven R. Mallory, *Software Development and Quality Assurance for the Healthcare Manufacturing Industries*, Interpharm Press,Inc., 1994. ISBN 0-935184-58-9.

Brian Marick, *The Craft of Software Testing*, Prentice Hall PTR, 1995. ISBN 0-13-177411-5.

Steve McConnell, *Rapid Development*, Microsoft Press, 1996. ISBN 1-55615-900-5.

Glenford J. Myers, *The Art of Software Testing*, John Wiley & Sons, 1979. ISBN 0-471-04328-1.

Peter G. Neumann, *Computer Related Risks*, ACM Press/Addison-Wesley Publishing Co., 1995. ISBN 0-201-55805-X.

Daniel Olivier, *Conducting Software Audits, Auditing Software for Conformance to FDA Requirements*, Computer Application Specialists, San Diego, CA, 1994.

William Perry, *Effective Methods for Software Testing*, John Wiley & Sons, Inc. 1995. ISBN 0-471-06097-6.

William E. Perry, Randall W. Rice, *Surviving the Top Ten Challenges of Software Testing*, Dorset

House Publishing, 1997. ISBN 0-932633-38-2.

Roger S. Pressman, *Software Engineering, A Practitioner's Approach*, Third Edition, McGraw-Hill Inc., 1992. ISBN 0-07-050814-3.

Roger S. Pressman, *A Manager's Guide to Software Engineering*, McGraw-Hill Inc., 1993 ISBN 0-07-050820-8.

A. P. Sage, J. D. Palmer, *Software Systems Engineering*, John Wiley & Sons, 1990.

Joc Sanders, Eugene Curran, *Software Quality,* Addison-Wesley Publishing Co., 1994. ISBN 0-201-63198-9.

Ken Shumate, Marilyn Keller, *Software Specification and Design, A Disciplined Approach for Real-Time Systems*, John Wiley & Sons, 1992. ISBN 0-471-53296-7.

Dennis D. Smith, *Designing Maintainable Software*, Springer-Verlag, 1999. ISBN 0-387-98783-5.

Ian Sommerville, *Software Engineering*, Third Edition, Addison Wesley Publishing Co., 1989. ISBN 0-201-17568-1.

Karl E. Wiegers, *Creating a Software Engineering Culture*, Dorset House Publishing, 1996. ISBN 0-932633-33-1.

Karl E. Wiegers, *Software Inspection, Improving Quality with Software Inspections*, Software Development, April 1995, pages 55-64.

Karl E. Wiegers, *Software Requirements*, Microsoft Press, 1999. ISBN 0-7356-0631-5.

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Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
August 2001
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Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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Internet: http://www.fda.gov/cber/guidelines.htm.
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U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry[1]
Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

I. INTRODUCTION (1)

A. Objective (1.1)

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess.

In this guidance, the term *manufacturing* is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this guidance, the term *should* identifies recommendations that, when followed, will ensure compliance with CGMPs. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes. For the purposes of this guidance, the terms *current good manufacturing practices* and *good manufacturing practices* are equivalent.

[1] This guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers in subheadings reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000.

The guidance as a whole does not cover safety aspects for the personnel engaged in manufacturing, nor aspects related to protecting the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guidance is not intended to define registration and/or filing requirements or modify pharmacopoeial requirements. This guidance does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents should be met.

B. Regulatory Applicability (1.2)

Within the world community, materials may vary as to their legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance.

C. Scope (1.3)

This guidance applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidances for drug (medicinal) products as defined by local authorities.

This guidance covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section XVIII (18).

This guidance excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance. In addition, the guidance does not apply to medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), or radiopharmaceuticals.

Section XIX (19) contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An *API starting material* is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under

contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which API starting materials are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API starting material is normally introduced into the process.

From this point on, appropriate GMP as defined in this guidance should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. However, all steps shown may not need to be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling, micronizing) should be conducted according to this guidance.

This GMP guidance does not apply to steps prior to the introduction of the defined API starting material.

Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	**Application of this guidance to steps (shown in gray) used in this type of manufacturing**				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establish-ment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establish-ment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

II. QUALITY MANAGEMENT (2)

A. Principles (2.1)

Quality should be the responsibility of all persons involved in manufacturing.

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

There should be a quality unit(s) that is independent of production and that fulfills both quality assurance *(QA)* and quality control *(QC)* responsibilities. The quality unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

The persons authorized to release intermediates and APIs should be specified.

All quality-related activities should be recorded at the time they are performed.

Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section X (10) or the use of raw materials or intermediates pending completion of evaluation).

Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

B. Responsibilities of the Quality Unit(s) (2.2)

The quality unit(s) should be involved in all quality-related matters.

The quality unit(s) should review and approve all appropriate quality-related documents.

The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company

2. Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution

4. Making sure that critical deviations are investigated and resolved

5. Approving all specifications and master production instructions

6. Approving all procedures affecting the quality of intermediates or APIs

7. Making sure that internal audits (self-inspections) are performed

8. Approving intermediate and API contract manufacturers

9. Approving changes that potentially affect intermediate or API quality

10. Reviewing and approving validation protocols and reports

11. Making sure that quality-related complaints are investigated and resolved

12. Making sure that effective systems are used for maintaining and calibrating critical equipment

13. Making sure that materials are appropriately tested and the results are reported

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates, where appropriate

15. Performing product quality reviews (as defined in Section 2.5)

C. Responsibility for Production Activities (2.3)

The responsibility for production activities should be described in writing and should include, but not necessarily be limited to:

1. Preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures

2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions

3. Reviewing all production batch records and ensuring that these are completed and signed

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded

5. Making sure that production facilities are clean and, when appropriate, disinfected

6. Making sure that the necessary calibrations are performed and records kept

7. Making sure that the premises and equipment are maintained and records kept

8. Making sure that validation protocols and reports are reviewed and approved

9. Evaluating proposed changes in product, process or equipment

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified

D. Internal Audits (Self Inspection) (2.4)

To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

E. Product Quality Review (2.5)

Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or nonconformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program
- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

III. PERSONNEL (3)

A. Personnel Qualifications (3.1)

There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

B. Personnel Hygiene (3.2)

Personnel should practice good sanitation and health habits.

Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

Personnel should avoid direct contact with intermediates or APIs.

Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

C. Consultants (3.3)

Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

IV. BUILDINGS AND FACILITIES (4)

A. Design and Construction (4.1)

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate.

Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
- Quarantine before release or rejection of intermediates and APIs
- Sampling of intermediates and APIs
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials
- Production operations
- Packaging and labeling operations
- Laboratory operations

Adequate and clean washing and toilet facilities should be provided for personnel. These facilities should be equipped with hot and cold water, as appropriate, soap or detergent, air dryers, or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process, intermediate, or API.

B. Utilities (4.2)

All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

C. Water (4.3)

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to ensure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for

physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

D. Containment (4.4)

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another.

Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

E. Lighting (4.5)

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

F. Sewage and Refuse (4.6)

Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

G. Sanitation and Maintenance (4.7)

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

V. PROCESS EQUIPMENT (5)

A. Design and Construction (5.1)

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Production equipment should only be used within its qualified operating range.

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter the quality of APIs or intermediates beyond the official or other established specifications. Any deviations from this practice should be evaluated to ensure that there are no detrimental effects on the material's fitness for use. Wherever possible, food grade lubricants and oils should be used.

Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

B. Equipment Maintenance and Cleaning (5.2)

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment
- Cleaning schedules, including, where appropriate, sanitizing schedules
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
- Instructions for the removal or obliteration of previous batch identification
- Instructions for the protection of clean equipment from contamination prior to use
- Inspection of equipment for cleanliness immediately before use, if practical
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate

Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Equipment should be identified as to its contents and its cleanliness status by appropriate means.

C. Calibration (5.3)

Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Equipment calibrations should be performed using standards traceable to certified standards, if they exist.

Records of these calibrations should be maintained.

The current calibration status of critical equipment should be known and verifiable.

Instruments that do not meet calibration criteria should not be used.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an effect on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

D. Computerized Systems (5.4)

GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.

Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

Written procedures should be available for the operation and maintenance of computerized systems.

Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Changes to computerized systems should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Data can be recorded by a second means in addition to the computer system.

VI. DOCUMENTATION AND RECORDS (6)

A. Documentation System and Specifications (6.1)

All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.

The issuance, revision, superseding, and withdrawal of all documents should be controlled by maintaining revision histories.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still legible.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain

other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality. Acceptance criteria should be established and documented for in-process controls.

If electronic signatures are used on documents, they should be authenticated and secure.

B. Equipment Cleaning and Use Record (6.2)

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

If equipment is dedicated to manufacturing one intermediate or API, individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

C. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials (6.3)

Records should be maintained including:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt

- The results of any test or examination performed and the conclusions derived from this

- Records tracing the use of materials

- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications

- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Master (approved) labels should be maintained for comparison to issued labels.

D. Master Production Instructions (Master Production and Control Records) (6.4)

To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified
- The production location and major production equipment to be used
- Detailed production instructions, including the:

  - sequences to be followed

  - ranges of process parameters to be used

  - sampling instructions and in-process controls with their acceptance criteria, where appropriate

  - time limits for completion of individual processing steps and/or the total process, where appropriate

  - expected yield ranges at appropriate phases of processing or time
- Where appropriate, special notations and precautions to be followed, or cross-references to these
- The instructions for storage of the intermediate or API to ensure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

E. Batch Production Records (Batch Production and Control Records) (6.5)

Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to ensure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is

produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed
- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

F. Laboratory Control Records (6.6)

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
- A statement of or reference to each test method used

- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
- A complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) the tests were performed
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
- All stability testing performed on APIs
- Out-of-specification (OOS) investigations

G. Batch Production Record Review (6.7)

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

VII. MATERIALS MANAGEMENT (7)

A. General Controls (7.1)

There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

Materials should be purchased against an agreed specification, from a supplier, or suppliers, approved by the quality unit(s).

If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

B. Receipt and Quarantine (7.2)

Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier

Large storage containers and their attendant manifolds, filling, and discharge lines should be appropriately identified.

Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

C. Sampling and Testing of Incoming Production Materials (7.3)

At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below. A *supplier's certificate of analysis* can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based on a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

D. Storage (7.4)

Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

E. Re-evaluation (7.5)

Materials should be re-evaluated, as appropriate, to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

VIII. PRODUCTION AND IN-PROCESS CONTROLS (8)

A. Production Operations (8.1)

Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code
- Receiving or control number
- Weight or measure of material in the new container
- Re-evaluation or retest date if appropriate

Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Other critical activities should be witnessed or subjected to an equivalent control.

Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Any deviation should be documented and explained. Any critical deviation should be investigated.

The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

B. Time Limits (8.2)

If time limits are specified in the master production instruction (see 6.40), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

C. In-process Sampling and Controls (8.3)

Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data.

The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

Critical in-process controls (and critical process monitoring), including control points and methods, should be stated in writing and approved by the quality unit(s).

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

D. Blending Batches of Intermediates or APIs (8.4)

For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

Acceptable blending operations include, but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch

Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.

The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

E. Contamination Control (8.5)

Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials.

Precautions to avoid contamination should be taken when APIs are handled after purification.

IX. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES (9)

A. General (9.1)

There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials.

Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

B. Packaging Materials (9.2)

Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.

C. Label Issuance and Control (9.3)

Access to the label storage areas should be limited to authorized personnel.

Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

Obsolete and out-dated labels should be destroyed.

Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

A printed label representative of those used should be included in the batch production record.

D. Packaging and Labeling Operations (9.4)

There should be documented procedures designed to ensure that correct packaging materials and labels are used.

Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API.

If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, special transport conditions, and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

X. STORAGE AND DISTRIBUTION (10)

A. Warehousing Procedures (10.1)

Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

B. Distribution Procedures (10.2)

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

XI. LABORATORY CONTROLS (11)

A. General Controls (11.1)

The independent quality unit(s) should have at its disposal adequate laboratory facilities.

There should be documented procedures describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

Reagents and standard solutions should be prepared and labeled following written procedures. *Use by* dates should be applied, as appropriate, for analytical reagents or standard solutions.

Primary reference standards should be obtained, as appropriate, for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Where a primary reference standard is not available from an officially recognized source, an *in-house primary standard* should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

B. Testing of Intermediates and APIs (11.2)

For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH guidance Q6B.

The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

C. Validation of Analytical Procedures - See Section 12. (11.3)

D. Certificates of Analysis (11.4)

Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

Information on the name of the intermediate or API including, where appropriate, its grade, the batch number, and the date of release should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address, and telephone number of the repacker/reprocessor and reference the name of the original manufacturer.

If new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

E. Stability Monitoring of APIs (11.5)

A documented, on-going testing program should be established to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

The test procedures used in stability testing should be validated and be stability indicating.

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in small-scale drums of similar or identical material composition to the market drums.

Normally, the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.

Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9-month testing) can be considered.

Where appropriate, the stability storage conditions should be consistent with the ICH guidances on stability.

F. Expiry and Retest Dating (11.6)

When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).

An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.

A representative sample should be taken for the purpose of performing a retest.

G. Reserve/Retention Samples (11.7)

The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the batch, whichever is longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.

The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

XII. VALIDATION (12)

A. Validation Policy (12.1)

The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.

The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes
- Identifying process parameters that could affect the critical quality attributes of the API
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

Validation should extend to those operations determined to be critical to the quality and purity of the API.

B. Validation Documentation (12.2)

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Any variations from the validation protocol should be documented with appropriate justification.

C. Qualification (12.3)

Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose
- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements

- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

D. Approaches to Process Validation (12.4)

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

There are three approaches to validation. Prospective validation is the preferred approach, but there are situations where the other approaches can be used. These approaches and their applicability are discussed here.

Prospective validation should normally be performed for all API processes as defined in 12.1. Prospective validation of an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

An exception can be made for retrospective validation of well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1. Critical quality attributes and critical process parameters have been identified

2. Appropriate in-process acceptance criteria and controls have been established

3. There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability

4. Impurity profiles have been established for the existing API

Batches selected for retrospective validation should be representative of all batches produced during the review period, including any batches that failed to meet specifications, and should be sufficient in number

to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

E. Process Validation Program (12.5)

The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to, or better than, historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

F. Periodic Review of Validated Systems (12.6)

Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

G. Cleaning Validation (12.7)

Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

Equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

H. Validation of Analytical Methods (12.8)

Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

XIII. CHANGE CONTROL (13)

A formal change control system should be established to evaluate all changes that could affect the production and control of the intermediate or API.

Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

Current dosage form manufacturers should be notified of changes from established production and process control procedures that can affect the quality of the API.

XIV. REJECTION AND RE-USE OF MATERIALS (14)

A. Rejection (14.1)

Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

B. Reprocessing (14.2)

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and over-reacted materials.

C. Reworking (14.3)

Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.

Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, a report can be written and the batch released once it is found to be acceptable.

Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

D. Recovery of Materials and Solvents (14.4)

Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials.

Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

E. Returns (14.5)

Returned intermediates or APIs should be identified as such and quarantined.

If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

XV. COMPLAINTS AND RECALLS (15)

All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

Complaint records should include:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the API)

- Date complaint is received
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent)
- Final decision on intermediate or API batch or lot

Records of complaints should be retained to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)

All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

A contract should permit a company to audit its contractor's facilities for compliance with GMP.

Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

XVII. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS (17)

A. Applicability (17.1)

This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.

All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this guidance.

B. Traceability of Distributed APIs and Intermediates (17.2)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

C. Quality Management (17.3)

Agents, brokers, traders, distributors, repackers, or relabelers should establish, document and implement an effective system of managing quality, as specified in Section 2.

D. Repackaging, Relabeling, and Holding of APIs and Intermediates (17.4)

Repackaging, relabeling, and holding APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance, to avoid mix-ups and loss of API or intermediate identity or purity.

Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

E. Stability (17.5)

Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

F. Transfer of Information (17.6)

Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context *authorized* refers to authorized by the manufacturer.)

The specific guidance for certificate of analysis included in Section 11.4 should be met.

G. Handling of Complaints and Recalls (17.7)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original API or intermediate manufacturer to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original API or intermediate manufacturer (including date and information provided).

H. Handling of Returns (17.8)

Returns should be handled as specified in Section 14.5. The agents, brokers, traders, distributors, repackers, or relabelers should maintain documentation of returned APIs and intermediates.

XVIII. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION (18)

A. General (18.1)

Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for *classical* processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

The term *biotechnological process* (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

The term *classical fermentation* refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by *classical fermentation* are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

Appropriate controls should be established at all stages of manufacturing to ensure intermediate and/or API quality. While this guidance starts at the cell culture/fermentation step, prior steps (e.g., cell banking) should be performed under appropriate process controls. This guidance covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for determining environmental quality and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

In general, process controls should take into account:

- Maintenance of the working cell bank (where appropriate)
- Proper inoculation and expansion of the culture
- Control of the critical operating parameters during fermentation/cell culture
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity, where appropriate
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production
- Viral safety concerns as described in ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*

Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

B. Cell Bank Maintenance and Record Keeping (18.2)

Access to cell banks should be limited to authorized personnel.

Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

Records of the use of the vials from the cell banks and storage conditions should be maintained.

Where appropriate, cell banks should be periodically monitored to determine suitability for use.

See ICH guidance Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

C. Cell Culture/Fermentation (18.3)

Where cell substrates, media, buffers, and gases are to be added under aseptic conditions, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent

transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

Personnel should be appropriately gowned and take special precautions handling the cultures.

Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, sanitized, or sterilized.

Culture media should be sterilized before use, when necessary, to protect the quality of the API.

Appropriate procedures should be in place to detect contamination and determine the course of action to be taken. Procedures should be available to determine the impact of the contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified, as appropriate, and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

Records of contamination events should be maintained.

Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

D. Harvesting, Isolation and Purification (18.4)

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption should be performed in equipment and areas designed to minimize the risk of contamination.

Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

E. Viral Removal/Inactivation steps (18.5)

See ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

XIX. APIs FOR USE IN CLINICAL TRIALS (19)

A. General (19.1)

Not all the controls in the previous sections of this guidance are appropriate for the manufacture of a new API for investigational use during its development. Section XIX (19) provides specific guidance unique to these circumstances.

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

B. Quality (19.2)

Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch.

A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

Process and quality problems should be evaluated.

Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

C. Equipment and Facilities (19.3)

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

D. Control of Raw Materials (19.4)

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

E. Production (19.5)

The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

F. Validation (19.6)

Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification ensures API quality during this development phase.

Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

G. Changes (19.7)

Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

H. Laboratory Controls (19.8)

While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

I. Documentation (19.9)

A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY (20)

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) ***(or Drug Substance):*** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden: The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with results produced by a reference or traceable standard over an appropriate range of measurements.

Computer System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging, or repackaging, storage or transport.

Contract Manufacturer: A manufacturer who performs some aspect of manufacturing on behalf of the original manufacturer.

Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination: Contamination of a material or product with another material or product.

Deviation: Departure from an approved instruction or established standard.

Drug (Medicinal) Product: The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance: See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions and after which it should not be used.

Impurity: Any component present in the intermediate or API that is not the desired entity.

Impurity Profile: A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control): Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this guidance only addresses those intermediates produced after the point that a company has defined as the point at which the production of the API begins.)

Lot: See Batch

Lot Number: See *Batch Number*

Manufacture: All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Material: A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It can be used for further processing.

Packaging Material: Any material intended to protect an intermediate or API during storage and transport.

Procedure: A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids: Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control: See ***In-Process Control.***

Production: All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA): The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): Checking or testing that specifications are met.

Quality Unit(s): An organizational unit independent of production that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary: A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete, is considered to be part of the normal process, and is not reprocessing.

Retest Date: The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed): See definition for signed.

Signed (signature): The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent: An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. *Conformance to specification* means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation Protocol: A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and/or operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical: The quantity that would be produced at any appropriate phase of production based upon the quantity of material to be used, in the absence of any loss or error in actual production.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current *Step 4* version
dated 9 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q9
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QUALITY RISK MANAGEMENT

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 9 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

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QUALITY RISK MANAGEMENT

1. INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate

industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

2. SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).

3. PRINCIPLES OF QUALITY RISK MANAGEMENT

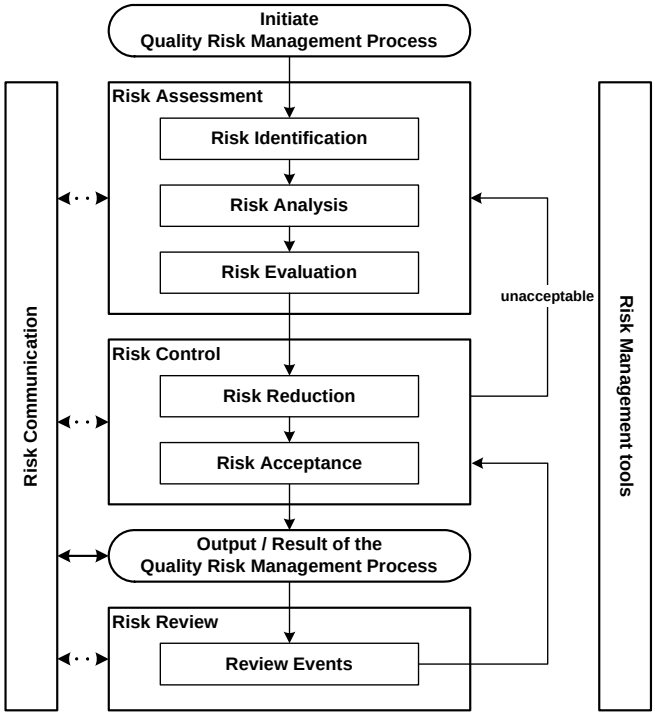
Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4. GENERAL QUALITY RISK MANAGEMENT PROCESS

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

4.1 Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.

4.2 Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

4.3 Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4 Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.5 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

4.6 Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

5. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

6. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be

used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management.

Examples for industry operations and activities (see Annex II):

- Development;
- Facility, equipment and utilities;
- Materials management;
- Production;
- Laboratory control and stability testing;
- Packaging and labeling.

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities.

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

7. DEFINITIONS

Decision Maker(s):

Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability:

The ability to discover or determine the existence, presence, or fact of a hazard.

Harm:

Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard:

The potential source of harm (ISO/IEC Guide 51).

Product Lifecycle:

All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality:

The degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System:

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements:

The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk:

The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance:

The decision to accept risk (ISO Guide 73).

Risk Analysis:

The estimation of the risk associated with the identified hazards.

Risk Assessment:

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication:

The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control:

Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation:

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification:

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Reduction:

Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review:

Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity:

A measure of the possible consequences of a hazard.

Stakeholder:

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend:

A statistical term referring to the direction or rate of change of a variable(s).

8. REFERENCES

ICH Q8 Pharmaceutical Development.

ISO/IEC Guide 73:2002 - Risk Management - Vocabulary - Guidelines for use in Standards.

ISO/IEC Guide 51:1999 - Safety Aspects - Guideline for their inclusion in standards.

Process Mapping by the American Productivity & Quality Center, 2002, ISBN 1928593739.

IEC 61025 - Fault Tree Analysis (FTA).

IEC 60812 Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA).

Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983.

Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press, ISBN 0849319102.

The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996, ISBN 0527763209.

WHO Technical Report Series No 908, 2003, Annex 7 *Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals*.

IEC 61882 - Hazard Operability Analysis (HAZOP).

ISO 14971:2000 - Application of Risk Management to Medical Devices.

ISO 7870:1993 - Control Charts.

ISO 7871:1997 - Cumulative Sum Charts.

ISO 7966:1993 - Acceptance Control Charts.

ISO 8258:1991 - Shewhart Control Charts.

What is Total Quality Control?; The Japanese Way, Kaoru Ishikawa (Translated by David J. Liu), 1985, ISBN 0139524339.

Annex I: Risk Management Methods and Tools

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts;
- Check Sheets;
- Process Mapping;
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited

to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process;

(2) determine the critical control points;

(3) establish critical limits;

(4) establish a system to monitor the critical control points;

(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;

(6) establish system to verify that the HACCP system is working effectively;

(7) establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control Charts, for example:
  - Acceptance Control Charts (see ISO 7966);
  - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873);
  - Cumulative Sum Charts (see ISO 7871);
  - Shewhart Control Charts (see ISO 8258);
  - Weighted Moving Average.
- Design of Experiments (DOE);
- Histograms;
- Pareto Charts;
- Process Capability Analysis.

Annex II: Potential Applications for Quality Risk Management

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations;

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness);

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc;

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements;
- Overall compliance status and history of the company or facility;
- Robustness of a company's quality risk management activities;
- Complexity of the site;
- Complexity of the manufacturing process;
- Complexity of the product and its therapeutic significance;
- Number and significance of quality defects (e.g., recall);
- Results of previous audits/inspections;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches);

- Test results of official control laboratories.

Periodic review

To select, evaluate and interpret trend results of data within the product quality review;

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

Change management / change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing;

To evaluate the impact of the changes on the availability of the final product;

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers;

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1);

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings;

To determine the appropriateness and type of post-inspection regulatory follow-up;

To evaluate information submitted by industry including pharmaceutical development information;

To evaluate impact of proposed variations or changes;

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality Risk Management as Part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:

- reduce product and material defects;
- reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;

To make use of the "design space" concept (see ICH Q8).

II.4 Quality Risk Management for Facilities, Equipment and Utilities

Design of facility / equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel;
- minimize contamination;
- pest control measures;
- prevention of mix-ups;
- open versus closed equipment;
- clean rooms versus isolator technologies;
- dedicated or segregated facilities / equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns);

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

Qualification of facility/equipment/utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production);

To determine acceptable (specified) cleaning validation limits.

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules.

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);

To determine the extent of validation, e.g.,

- identification of critical performance parameters;
- selection of the requirements and design;
- code review;
- the extent of testing and test methods;
- reliability of electronic records and signatures.

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);

To determine appropriateness of reprocessing, reworking, use of returned goods.

Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods;

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation);

To distinguish between critical and non-critical process steps to facilitate design of a validation study.

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

II.8 Quality Risk Management as Part of Packaging and Labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of container closure system

To determine the critical parameters of the container closure system.

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

Guidance for Industry
Computerized Systems Used in Clinical Trials

DRAFT GUIDANCE — ERRATUM

On line 563 of this draft guidance, reference is made to Compliance Policy Guide (CPG) # 7130.13. This is incorrect. The CPG number should be 7150.13.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

September 2004
Compliance

Revision 1

Guidance for Industry
Computerized Systems Used in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Patricia M. Beers Block 301-827-3340.

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Guidance for Industry

Computerized Systems Used in Clinical Trials

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Guidance for Industry[1]
Computerized Systems Used in Clinical Trials

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance about computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained and/or submitted to the Food and Drug Administration (FDA) These data form the basis for the Agency's decisions regarding the safety and effectiveness of new human and animal drugs, biological products, medical devices, and certain food and color additives. Because the data have broad public health significance, they are expected to be of the highest quality and integrity. This guidance document addresses long-standing FDA regulations concerning clinical trial records. It also addresses requirements of the Electronic Records/Electronic Signatures rule (21 CFR part 11).[2]

Once finalized, this document will supersede the guidance of the same name issued in April 1999. Revisions will make it consistent with Agency policy as reflected in the guidance for industry on *Part 11, Electronic Records; Electronic Signatures — Scope and Application,* which issued in August 2003, and the Agency's international harmonization efforts.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by an Agency working group representing the Bioresearch Monitoring Program Managers for each Center within the Food and Drug Administration, the Office of Regulatory Affairs, and the Office of the Commissioner.

[2] Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the requirements of Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in Agency regulations.

[3] In August 2003, FDA issued the guidance for industry entitled *Part 11, Electronic Records; Electronic Signatures-Scope and Application* clarifying that the Agency intended to interpret the scope of part 11 narrowly and to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying. In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued *E6 Good Clinical Practice: Consolidated Guidance*.

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA has the authority to inspect all records relating to clinical investigations conducted under 21 CFR 312, 511.1(b), and 812 , regardless of how they were created or maintained (e.g., §§ 312.58, 312.68, and 812.145). FDA established the Bioresearch Monitoring (BIMO) Program of inspections and audits to monitor the conduct and reporting of clinical trials to ensure that supporting data from these trials meet the highest standards of quality and integrity, and conform to FDA's regulations. FDA's acceptance of data from clinical trials for decision-making purposes depends on FDA's ability to verify the quality and integrity of the data during FDA on-site inspections and audits. To be acceptable, the data should meet certain fundamental elements of quality whether collected or recorded electronically or on paper. For example, data should be attributable, legible, contemporaneous, original[4] and accurate.

This guidance addresses how Agency expectations and regulatory requirements regarding data quality might be satisfied where computerized systems are being used to create, modify, maintain, archive, retrieve, or transmit clinical data. Although the primary focus of this guidance is on computerized systems used at clinical sites to collect data, the principles set forth may also be appropriate for computerized systems belonging to contract research organizations, data management centers, and sponsors. Persons using the data from computerized systems should have confidence that the data are no less reliable than data in paper form.

Computerized medical devices, diagnostic laboratory instruments, and instruments in analytical laboratories that are used in clinical trials are not the subject of this guidance. This guidance does not address electronic submissions or methods of their transmission to the Agency, except to the degree to which these records comply with Part 11.

The principles in this guidance may be applied where supporting data or source documents[5] are created (1) in hardcopy and later entered into a computerized system, (2) by direct entry by a human into a computerized system, and (3) automatically by a computerized system.

III. GENERAL PRINCIPLES

[4] FDA is allowing original documents to be replaced by certified copies provided the copies are identical and have been verified as such. (see FDA Compliance Policy Guide # 7130.13). See “Definitions” section for a definition of original data.

[5] Under 21 CFR 312.62 (b) reference is made to records that are part of case histories as “supporting data;” the ICH *E6 Good Clinical Practice* consolidated guidance uses the term "source documents." These terms describe the same information and have been used interchangeably in this guidance.

The Agency recommends the following general principles with regard to computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained and/or submitted to FDA.

1. We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.

2. For each study, we recommend that documentation identify what software and hardware are to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. We also recommend that this documentation be retained as part of the study records.

3. We recommend that computerized systems be designed (1) so that all requirements assigned to these systems in a study protocol are satisfied (e.g., data are recorded in metric units, the study blinded) and (2) to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission.

4. It is important to design a computerized system in such a manner so that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems.

5. Under 21 CFR 312.62 , 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b) and § 812, respectively, for a period of time specified in these regulations. Retaining the original source document or a certified copy of the source document at the site where the investigation was conducted can assist in meeting these regulatory requirements. It can also assist in the reconstruction and evaluation of the trial throughout and after the completion of the trial.

6. When original observations are entered directly into a computerized system, the electronic record is the source document.

7. Records relating to an investigation must be adequate and accurate in the case of investigational new drug applications (INDs) (see § 312.57 and § 312.62), complete in the case of new animal drugs for investigational use (INADs) (see §511.1(b)(7)(ii)), and accurate, complete and current in the case of investigational device exemptions (IDEs) (see § 812.140(a) and § 812.140(b)). An audit trail that is electronic or consists of other physical, logical, or procedural security measures to ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred may be needed to facilitate compliance with applicable records regulations. Firms should determine and document the need for audit trails based on a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities. We recommend that audit trials or other security methods used to capture electronic record activities document who made the changes, when, and why changes were made to the electronic record.

8. We recommend that data be retrievable in such a fashion that all information regarding each individual subject in a study is attributable to that subject.

9. To ensure the authenticity and integrity of electronic records, it is important that security measures be in place to prevent unauthorized access to the data in the electronic record and to the computerized system.

IV. OVERALL APPROACH TO MEETING PART 11 REQUIREMENTS

As described in the FDA guidance entitled *Part 11, Electronic Records; Electronic Signatures-Scope and Application* (August 2003), while the re-examination of part 11 is underway, FDA intends to exercise enforcement discretion with respect to part 11 requirements for validation, audit trail, record retention, and record copying. That is, FDA does not intend to take enforcement action to enforce compliance with these requirements of part 11 while the agency re-examines part 11. Note that part 11 remains in effect and that the exercise of enforcement discretion applies only to the extent identified in the FDA guidance on part 11. Also, records must still be maintained or submitted in accordance with the underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act (Act), the Public Health Service Act (PHS Act), and FDA regulations (other than part 11), which are referred to in this guidance document as *predicate rules*, and FDA can take regulatory action for noncompliance with such predicate rules.[6]

Specific details about the Agency's approach to enforcing part 11 can be found in the *Part 11 Scope and Application* guidance.

V. STANDARD OPERATING PROCEDURES

We recommend that standard operating procedures (SOPs) pertinent to the use of the computerized system be available on site. We recommend that SOPs be established for the following:

- System Setup/Installation
- Data Collection and Handling
- System Maintenance
- Data Backup, Recovery, and Contingency Plans
- Security
- Change Control
- Alternative Recording Methods (in the case of system unavailability)

VI. DATA ENTRY

A. Computer Access Controls

To ensure that individuals have the authority to proceed with data entry, data entry systems must be designed to limit access so that only authorized individuals are able to input data

[6] This term refers to underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the PHS Act, and FDA regulations (other than 21 CFR Part 11). Regulations governing good clinical practice and human subject protection can be found at 21 CFR parts 50, 56, 312, 511, and 812. See Definitions section at the end of this document listing definitions of this and other terms used in this guidance.

(§ 11.10(d)).[7] Examples of methods for controlling access include using combined identification codes/passwords or biometric-based identification at the start of a data entry session. Controls and procedures must be in place that are designed to ensure the authenticity and integrity of electronic records created, modified, maintained, or transmitted using the data entry system (§ 11.10). Therefore, we recommend that each user of the system have an individual account into which the user logs-in at the beginning of a data entry session, inputs information (including changes) on the electronic record, and logs out at the completion of data entry session.

We recommend that individuals work only under their own password or other access key and not share these with others. We recommend that individuals not be allowed to log onto the system to provide another person access to the system. We also recommend that passwords or other access keys be changed at established intervals.

When someone leaves a workstation, we recommend that the SOP require that person to log off the system. Alternatively, an automatic log off may be appropriate for long idle periods. For short periods of inactivity, we recommend that some kind of automatic protection be installed against unauthorized data entry. An example could be an automatic screen saver that prevents data entry until a password is entered.

B. Audit Trails or other Security Measures

Section 11.10(e) requires persons who use electronic record systems to maintain an audit trail as one of the procedures to protect the authenticity, integrity, and, when appropriate, the confidentiality of electronic records. As clarified in the *Part 11 Scope and Application* guidance, however, the Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10(e), (k)(2) and any corresponding requirement in § 11.30). Persons must still comply with all applicable predicate rule requirements for clinical trials, including, for example, that records related to the conduct of the study must be adequate and accurate (§§ 312.57, 312.62, and 812.140). It is therefore important to keep track of all changes made to information in the electronic records that document activities related to the conduct of the trial. Computer-generated, time-stamped audit trails or information related to the creation, modification, or deletion of electronic records may be useful to ensure compliance with the appropriate predicate rule.

In addition, clinical investigators must, upon request by FDA, at reasonable times, permit agency employees to have access to, and copy and verify any required records or reports made by the investigator (§§ 312.68, 511.1(b)(7)(ii) and 812.145). In order for the Agency to review and copy this information, FDA personnel should be able to review audit trails or other documents that track electronic record activities both at the study site and at any other location where associated electronic study records are maintained. To enable FDA's review, information about the creation, modification, or deletion of electronic records should be created incrementally, and in chronological order. To facilitate FDA's inspection of this information, we recommend that clinical investigators retain either the original or a certified copy of any documentation created to track electronic records activities.

[7] As FDA announced in the *Part 11 Scope and Application* guidance, we intend to enforce certain controls for closed systems in § 11.10, including §11.10(d).

Even if there are no applicable predicate rule requirements, it may be important to have computer-generated, time-stamped audit trails or other physical, logical, or procedural security measures to ensure the trustworthiness and reliability of electronic records. We recommend that any decision on whether to apply computer-generated audit trails or other appropriate security measures be based on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on data quality and record integrity. Firms should determine and document the need for audit trails based on a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities.

If you determine that audit trails or other appropriate security measures are needed to ensure electronic record integrity, we recommend that personnel who create, modify, or delete electronic records not be able to modify the documents or security measures used to track electronic record changes. We recommend that audit trials or other security methods used to capture electronic record activities document who made the changes, when, and why changes were made to the electronic record.

Some examples of methods for tracking changes to electronic records include:

- Computer-generated, time-stamped electronic audit trails.
- Signed and dated printed versions of electronic records that identify what, when, and by whom changes were made to the electronic record. When using this method, it is important that appropriate controls be utilized that ensure the accuracy of these records (e.g., sight verification that the printed version accurately captures all of the changes made to the electronic record).
- Signed and dated printed standard electronic file formatted versions (e.g., pdf, xml or sgml) of electronic records that identify what, when, and by whom changes were made to the electronic record.
- Procedural controls that preclude unauthorized personnel from creating, modifying, or deleting electronic records or the data contained therein.

C. Date/Time Stamps

We recommend that controls be put in place to ensure that the system's date and time are correct. The ability to change the date or time should be limited to authorized personnel and such personnel should be notified if a system date or time discrepancy is detected. We recommend that someone always document changes to date or time. We do not expect documentation of time changes that systems make automatically to adjust to daylight savings time conventions.

We also recommend that dates and times include the year, month, day, hour, and minute. The Agency encourages establishments to synchronize systems to the date and time provided by trusted third parties.

Clinical study computerized systems are likely be used in multi-center trials and may be located in different time zones. For systems that span different time zones, it is better to implement time stamps with a clear understanding of the time zone reference used. We recommend that system

documentation explain time zone references as well as zone acronyms or other naming conventions.

VII. SYSTEM FEATURES

The Agency recommends that a number of computerized system features be available to facilitate the collection, inspection, review, and retrieval of quality clinical data. Key features are described here.

A. Systems Used for Direct Entry of Data

We recommend that prompts, flags, or other help features be incorporated into the computerized system to encourage consistent use of clinical terminology and to alert the user to data that are out of acceptable range. We recommend against the use of features that automatically enter data into a field when the field is bypassed.

B. Retrieval of Data and Record Retention

FDA expects to be able to reconstruct a clinical study submitted to the agency. This means that documentation, such as that described in the General Principles, Sections III.1, III.2 and III.5, should fully describe and explain how data were obtained and managed and how electronic records were used to capture data. We suggest that your decision on how to maintain records be based on predicate rule requirements and that this documented decision be based on a justified risk assessment and a determination of the value of the records over time. As explained in the Part 11 Scope and Application guidance, FDA does not intend to object to required records that are archived in electronic format; nonelectronic media such as microfilm, microfiche, and paper; or to a standard electronic file format (such as PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of required records should preserve their original content and meaning. Paper and electronic record and signature components can co-exist (i.e., as a hybrid system) as long as the predicate requirements (21 CFR parts 50, 56, 312, 511, and 812) are met, and the content and meaning of those records are preserved.

It is not necessary to reprocess data from a study that can be fully reconstructed from available documentation. Therefore, actual application software, operation systems, and software development tools involved in processing of data or records do not need to be retained.

VIII. SYSTEM SECURITY

In addition to internal safeguards built into the computerized system, external safeguards should be put in place to ensure that access to the computerized system and to the data is restricted to authorized personnel as required by 21 CFR 11.10(d). We recommend that staff be kept thoroughly aware of system security measures and the importance of limiting access to authorized personnel.

SOPs should be developed and implemented for handling and storing the system to prevent unauthorized access. Controlling system access can be accomplished through the following provisions of part 11 that, as discussed in the part 11 guidance, FDA intends to continue to enforce:

- Operational system checks (§ 11.10(f));
- Authority checks (§ 11.10(g));
- Device (e.g., terminal) checks (§ 11.10(h)); and
- The establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures (§ 11.10(j)).

The Agency recommends that access to data be restricted and monitored through the system's software with its required log-on, security procedures, and audit trail (or other selected security measures to track electronic record activities). We recommend that procedures and controls be implemented to prevent the data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software.

We recommend that a cumulative record be available that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. We recommend that the record be kept in the study documentation, accessible at the site.

If a sponsor supplies computerized systems exclusively for clinical trials, we recommend that the systems remain dedicated to the purpose for which they were intended and validated. If a computerized system being used for a clinical study is part of a system normally used for other purposes, we recommend that efforts be made to ensure that the study software be logically and physically isolated as necessary to preclude unintended interaction with nonstudy software. If any of the software programs are changed, we recommend that the system be evaluated to determine the effect of the changes on logical security.

We recommend that controls be implemented to prevent, detect, and mitigate effects of computer viruses, worms, or other potentially harmful software code on study data and software.

IX. SYSTEM DEPENDABILITY

The Agency recommends that sponsors ensure and document that all computerized systems conform to their own established requirements for completeness, accuracy, reliability, and consistent intended performance.

We recommend that systems documentation be readily available at the site where clinical trials are conducted and provide an overall description of the computerized systems and the relationships among hardware, software, and physical environment.

As noted in the *Part 11 Scope and Application* guidance, the Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems. We suggest that your decision to validate computerized systems and the extent of the validation take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy,

reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, it may still be important to validate the system, based on criticality and risk, to ensure the accuracy, reliability, integrity, availability and authenticity of required records and signatures.

We recommend that you base your approach on a justified and documented risk assessment and determination of the potential of the system to affect data quality and record integrity. For example, in the case where data are directly entered into electronic records and the business practice is to rely on the electronic record, validation of the computerized system is important. However when a word processor is used to generate SOPs for use at the clinical site, validation would not be important.

If validation is required, FDA may ask to see the regulated company's documentation that demonstrates software validation. The study sponsor is responsible for making any such documentation available if requested at the time of inspection at the site where software is used. Clinical investigators are not generally responsible for validation unless they originated or modified software.

A. Legacy Systems

As noted in the *Part 11 Scope and Application* guidance, the Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were fully operational prior to August 20, 1997, the effective date of part 11, under the circumstances described below. These systems are also known as legacy systems. The Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was in operation before the part 11 effective date.
- The system met all applicable predicate rule requirements prior to the part 11 effective date.
- The system currently meets all applicable predicate rule requirements.
- There is documented evidence and justification that the system is fit for its intended use.

If a system has changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, part 11 controls should be applied to part 11 records and signatures pursuant to the enforcement policy expressed in the part 11 guidance. Please refer to the *Part 11 Scope and Application* guidance for further information.

B. Off-the-Shelf Software

While the Agency has announced that it intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems, persons must still comply with all predicate rule requirements for validation. We suggested in the guidance for industry on part 11 that the impact of computerized systems on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures be considered when you decide whether to validate, and noted that even absent a predicate rule requirement to validate a system, it might still be important to validate in some instances.

For most off-the-shelf software, the design level validation will have already been done by the company that wrote the software. Given the importance of ensuring valid clinical trial data, FDA suggests that the sponsor or contract research organization (CRO) have documentation (either original validation documents or on-site vendor audit documents) of this design level validation by the vendor and would itself have performed functional testing (e.g., by use of test data sets) and researched known software limitations, problems, and defect corrections. Detailed documentation of any additional validation efforts performed by the sponsor or CRO will preserve the findings of these efforts.

In the special case of database and spreadsheet software that is: (1) purchased off-the-shelf, (2) designed for and widely used for general purposes, (3) unmodified, and (4) not being used for direct entry of data, the sponsor or contract research organization may not have documentation of design level validation. FDA suggests that the sponsor or contract research organization perform functional testing (e.g., by use of test data sets) and research known software limitations, problems, and defect corrections.

In the case of off-the-shelf software, we recommend that the following be available to the Agency on request:

- A written design specification that describes what the software is intended to do and how it is intended to do it;
- A written test plan based on the design specification, including both structural and functional analysis; and
- Test results and an evaluation of how these results demonstrate that the predetermined design specification has been met.

Additional guidance on general software validation principles can be found in FDA's guidance entitled *General Principles of Software Validation; Final Guidance for Industry and FDA Staff.*

C. Change Control

FDA recommends that written procedures be put in place to ensure that changes to the computerized system, such as software upgrades, including security and performance patches, equipment, or component replacement, or new instrumentation, will maintain the integrity of the data and the integrity of protocols. We recommend that the effects of any changes to the system be evaluated and a decision made regarding whether, and if so, what level of validation activities related to those changes would be appropriate. We recommend that validation be performed for those types of changes that exceed previously established operational limits or design specifications. Finally, we recommend that all changes to the system be documented.

X. SYSTEM CONTROLS

The Agency recommends that appropriate system control measures be developed and implemented.

- Software Version Control

We recommend that measures be put in place to ensure that versions of software used to generate, collect, maintain, and transmit data are the versions that are stated in the systems documentation.

- Contingency Plans

We recommend that written procedures describe contingency plans for continuing the study by alternate means in the event of failure of the computerized system.

- Backup and Recovery of Electronic Records

When electronic formats are the only ones used to create and preserve electronic records, the Agency recommends that backup and recovery procedures be outlined clearly in SOPs and be sufficient to protect against data loss. We also recommend that records be backed up regularly in a way that would prevent a catastrophic loss and ensure the quality and integrity of the data. We recommend that records be stored at a secure location specified in the SOPs. Storage is typically offsite or in a building separate from the original records.

We recommend that backup and recovery logs be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.

Firms that rely on electronic and paper systems should determine the extent to which backup and recovery procedures are needed based on the need to meet predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on data quality and record integrity.

XI. TRAINING OF PERSONNEL

Under 21 CFR 11.10(i), firms using computerized systems must determine that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks.

The Agency recommends that training be provided to individuals in the specific operations with regard to computerized systems that they are to perform. We recommend that training be conducted by qualified individuals on a continuing basis, as needed, to ensure familiarity with the computerized system and with any changes to the system during the course of the study.

We recommend that employee education, training, and experience be documented.

XII. COPIES OF RECORDS AND RECORD INSPECTION

FDA has the authority to inspect all records relating to clinical investigations conducted under 21 CFR Parts 312 and 812, regardless of how the records were created or maintained (21 CFR

312.58, 312.68, and 812.145). Therefore, you should provide the FDA investigator with reasonable and useful access to records during an FDA inspection. As noted in the *Part 11, Electronic Records; Electronic Signatures- Scope and Application* guidance, the Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10(b) and any corresponding requirement in § 11.30). We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies available in a more common format (e.g., pdf, xml, or sgml formats)

Regardless of the method used to produce copies of electronic records, it is important that the copying process used produces copies that preserve the content and meaning of the record. For example, if you have the ability to search, sort, or trend records, copies given to FDA should provide the same capability if it is reasonable and technically feasible. FDA expects to inspect, review, and copy records in a human readable form at your site, using your hardware and following your established procedures and techniques for accessing records.

We recommend you contact the Agency if there is any doubt about what file formats and media the Agency can read and copy.

XIII. CERTIFICATION OF ELECTRONIC SIGNATURES

As required by 21 CFR 11.100(c), persons using electronic signatures to meet an FDA signature requirement must, prior to or at the time of such use, certify to the Agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

As set forth in § 11.100(c)(1), the certification must be submitted in paper, signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, Maryland 20857. The certification is to be submitted prior to or at the time electronic signatures are used. However, a single certification can be used to cover all electronic signatures used by persons in a given organization. This certification is created by persons to acknowledge that their electronic signatures have the same legal significance as their traditional handwritten signatures. See the following example of a certification statement:

> Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that ___[*name of organization*]__ intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

DEFINITIONS

The following is a list of definitions for terms as they are used in, and for the purposes of, this guidance document.

Attributable Data: Attributable data are those that can be traced to individuals responsible for observing and recording the data. In an automated system, attributability could be achieved by a computer system designed to identify individuals responsible for any input.

Audit Trail: An *audit trail* is a secure, computer generated, time-stamped electronic record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record.

Certified Copy: A copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original

Computerized System: A *computerized system* includes computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical trial.

Direct Entry: Recording data where an electronic record is the original capture of the data. Examples are the keying by an individual of original observations into the system, or automatic recording by the system of the output of a balance that measures subject's body weight.

Electronic Record: Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Electronic Signature: A computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

Original data: *Original data* are those values that represent the first recording of study data. FDA is allowing original documents and the original data recorded on those documents to be replaced by certified copies provided the copies are identical and have been verified as such. (see FDA Compliance Policy Guide # 7130.13

Predicate rule: This term refers to underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the PHS Act, and FDA regulations (other than 21 CFR part 11). Regulations governing good clinical practice and human subject protection can be found at 21 CFR parts 50, 56, 312, 511, and 812.

Software Validation: Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses and that the particular requirements implemented through the software can be consistently fulfilled. *Design level*

validation is that portion of the software validation that takes place in parts of the software life cycle before the software is delivered to the end user.

Source Documents: Original documents and records including, but not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Transmit: *Transmit* is to transfer data within or among clinical study sites, contract research organizations, data management centers, or sponsors. Other Agency guidance covers transmission from sponsors to the Agency.

584
585 **REFERENCES**
586
587

588 FDA, *21 CFR Part 11, "*Electronic Records; Electronic Signatures; Final Rule.*" Federal*
589 *Register* Vol. 62, No. 54, 13429, March 20, 1997.

590 FDA, *Compliance Program Guidance Manual,* "Compliance Program 7348.810 - Sponsors,
591 Contract Research Organizations and Monitors," October 30, 1998.

592 FDA, *Compliance Program Guidance Manual,* "Compliance Program 7348.811 - Bioresearch
593 Monitoring - Clinical Investigators," September 2, 1998.

594 FDA, *Glossary of Computerized System and Software Development Terminology*, 1995.

595 FDA, *Good Clinical Practice VICH GL9,* 2001.

596 FDA, *Guideline for the Monitoring of Clinical Investigations*, 1988.

597 FDA, *Information Sheets for Institutional Review Boards and Clinical Investigators,* 1998.

598 FDA, *Software Development Activities*, 1987.

599 International Conference on Harmonisation, "E6 Good Clinical Practice: Consolidated
600 Guideline," *Federal Register,* Vol. 62, No. 90, 25711, May 9, 1997.

601 FDA, *Part 11, Electronic Records; Electronic Signatures — Scope and Application*, 2003.

602 FDA, *General Principles of Software Validation; Guidance for Industry and FDA Staff,* 2002.

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Guidance for Industry

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Revision 1

Guidance for Industry

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

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Guidance for Industry[1]

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1) [2]

This guidance describes an approach to broader use of the ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products* (hereafter referred to as the parent guidance) and outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in climatic zones III and IV (Grimm 1985 and 1986, Schumacher 1974). This guidance, which was first published in November 2003, is revised to correct the guidance title on the first page of the document and two in-text references to Grimm.

A. Background (1.2)

The parent guidance describes the stability data package for the ICH tripartite regions (the European Union (EU), Japan, and the United States), which are in climatic zones I and II. The parent guidance can be followed to generate stability data packages for registration applications in other countries or regions in zones I and II. For territories in climatic zones III and IV, the data package as described in the parent guidance can be considered applicable except for certain

[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, February 2003.

storage conditions. An approach for classification of countries according to climatic zones I, II, III, and IV can be found in the literature (Dietz 1993, Grimm 1998).

The World Health Organization (WHO) has published a guideline "Stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms" (WHO Technical Report Series, No. 863, Annex 5), updated in the "Report of the thirty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations," Geneva, 22-26 October 2001. The WHO guideline describes stability testing recommendations, including storage conditions for all four climatic zones.

The stability testing recommendations in this guidance are based on the parent guidance and the WHO guideline. To harmonize with the long-term storage condition for zones III and IV, the intermediate storage condition in the *general case* for zones I and II in the parent guidance is changed to 30°C ± 2°C/65% relative humidity (RH) ± 5% RH. This condition of 30°C ± 2°C/65% RH ± 5% RH can also be a suitable alternative to 25°C ± 2°C/60% RH ± 5% RH as the long-term storage condition for zones I and II.

B. Scope of the Guidance (1.3)

This document is an annex to the parent guidance and recommends the long-term storage condition for stability testing of a new drug substance or drug product for a registration application in territories in climatic zones III and IV.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GUIDANCE (2)

A. Continuity With the Parent Guidance (2.1)

This guidance should be used in conjunction with the parent guidance and subsequently published annexes (Q1B, Q1C, Q1D, Q1E, Q5C).[3] The recommendations in the parent guidance and annexes should be followed unless specific alternatives are described within this guidance. The following sections of the parent guidance can be considered common to any territory in the world and are not reproduced here:

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency

[3] These ICH guidances are available on the Internet at www.fda.gov/cder/guidance/index.htm.

- Storage conditions for drug substance or product in a refrigerator
- Storage conditions for drug substance or product in a freezer
- Stability commitment
- Evaluation
- Statements/labeling

B. Storage Conditions (2.2)

1. General Case (2.2.1)

For the *general case* (as described in the parent guideline), the recommended long-term and accelerated storage conditions for climatic zones III and IV are shown below:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

No intermediate storage condition for stability studies is recommended for climatic zones III and IV. Therefore, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in the ICH guidance *Q1E Evaluation of Stability Data* are applied.

2. Aqueous-Based Drug Products Packaged in Semipermeable Containers (2.2.2)

For aqueous-based drug products packaged in semipermeable containers (as described in the parent guidance), the recommended long-term and accelerated storage conditions for climatic zones III and IV are shown below:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/35% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/not more than 25 % RH ± 5% RH	6 months

As described in the parent guidance, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio (see table below for examples). The ratio of water loss rates at a given temperature is calculated by the general formula (100 minus reference % RH) / (100 minus alternative % RH).

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

3. Tests at Elevated Temperature and/or Extremes of Humidity (2.2.3)

Special transportation and climatic conditions outside the storage conditions recommended in this guidance should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover extremely hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions (Grimm 1985 and 1986).

Stability testing at a high humidity condition (e.g., 25°C/80% RH) is recommended for solid dosage forms in water-vapor permeable packaging (e.g., tablets in PVC/aluminum blisters) intended to be marketed in territories with extremely high humidity conditions in zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapor (e.g., aluminum/aluminum blisters), stability testing at a storage condition of extremely high humidity is not considered necessary.

C. Additional Considerations (2.3)

If it cannot be demonstrated that the drug substance or drug product will remain within its acceptance criteria when stored at 30°C ± 2°C/65 % RH ± 5 % RH for the duration of the proposed retest period or shelf life, the following options should be considered: (1) a reduced retest period or shelf life, (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

REFERENCES (3)

Dietz, R., K. Feilner, F. Gerst, and W. Grimm, "Drug Stability Testing — Classification of countries according to climatic zone," *Drugs Made in Germany*, 36:99-103, 1993.

Grimm, W., "Storage Conditions for Stability Testing — Long term testing and stress tests," *Drugs Made in Germany*, 28:196-202, 1985 (Part I) and 29:39-47, 1986 (Part II).

Grimm, W., "Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV," *Drug Development and Industrial Pharmacy*, 24:313-325, 1998.

Schumacher, P., "Aktuelle Fragen zur Haltbarkeit von Arzneimitteln [Current questions on drug stability]," *Pharmazeutische Zeitung*, 119:321-324, 1974.

Guidance for Industry

Q1A(R2) Stability Testing of New Drug Substances and Products

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Contains Nonbinding Recommendations

Guidance for Industry[1]

Q1A(R2) Stability Testing of New Drug Substances and Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1)[2]

This guidance is the second revision of *Q1A Stability Testing of New Drug Substances and Products,* which was first published in September 1994 and revised in August 2001. The purpose of this revision is to harmonize the intermediate storage condition for zones I and II with the long-term condition for zones III and IV recommended in the ICH guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV.* The changes made in this second revision are listed in the attachment to this guidance.

A. Objectives of the Guidance (1.1)

This guidance is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan, and the United States. It does not seek to address the testing for registration in or export to other areas of the world. The guidance exemplifies the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

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[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

B. Scope of the Guidance (1.2)

The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guidance.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidances *Q1C Stability Testing for New Dosage Forms* and *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, respectively.

C. General Principles (1.3)

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the three regions of the EU, Japan, and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guidance addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EU, Japan, and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guidance and the labeling is in accord with national/regional requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GUIDANCE (2)

A. Drug Substance (2.1)

1. General (2.1.1)

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

2. Stress Testing (2.1.2)

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. The testing should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C) above that for accelerated testing), humidity (e.g., 75 percent relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH *Q1B Photostability Testing of New Drug Substances and Products*.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, such examination may not be necessary for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

3. Selection of Batches (2.1.3)

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

4. Container Closure System (2.1.4)

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

5. Specification (2.1.5)

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, is addressed in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and *Q6B*

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products. In addition, specification for degradation products in a drug substance is discussed in ICH *Q3A Impurities in New Drug Substances*.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed should depend on the results from validation studies.

6. Testing Frequency (2.1.6)

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

7. Storage Conditions (2.1.7)

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case should apply if the drug substance

is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.1.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and *significant change* occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Significant change for a drug substance is defined as failure to meet its specification.

b. Drug substances intended for storage in a refrigerator (2.1.7.2)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than

3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

c. Drug substances intended for storage in a freezer (2.1.7.3)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug substances intended for storage in a freezer, the retest period should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

d. Drug substances intended for storage below -20°C (2.1.7.4)

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

8. Stability Commitment (2.1.8)

When available long-term stability data on primary batches do not cover the proposed retest period granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the retest period.

Where the submission includes long-term stability data on three production batches covering the proposed retest period, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.

- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed retest period.

- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed retest period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

9. Evaluation (2.1.9)

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent, one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

10. Statements/Labeling (2.1.10)

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

B. Drug Product (2.2)

1. General (2.2.1)

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance, results from stability studies on the drug substance, and experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2. Photostability Testing (2.2.2)

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

3. Selection of Batches (2.2.3)

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

4. Container Closure System (2.2.4)

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and

container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

5. Specification (2.2.5)

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug product is addressed in ICH *Q3B Impurities in New Drug Products*.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

6. Testing Frequency (2.2.6)

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs (i.e., matrixing or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

7. Storage Conditions (2.2.7)

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and if full shelf life, long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.2.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are condcuted at 25°C ± 2°C/60% RH ± 5% RH and *significant change* occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, *significant change* for a drug product is defined as one or more of the following (as appropriate for the dosage form):

- A 5 percent change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- Any degradation product's exceeding its acceptance criterion
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.
- Failure to meet the acceptance criterion for pH
- Failure to meet the acceptance criteria for dissolution for 12 dosage units

b. Drug products packaged in impermeable containers (2.2.7.2)

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

c. Drug products packaged in semipermeable containers (2.2.7.3)

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term *	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.
** If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

When long-term studies are conducted at 25°C ± 2°C/40% RH ± 5% RH and significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed, as described under the general case, to evaluate the temperature effect at 30°C. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40 percent RH.

A 5 percent loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5 percent or more after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH may be appropriate if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation

coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature (e.g., 40°C), the calculated water loss rate during storage at NMT 25 percent RH is the water loss rate measured at 75 percent RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	**Reference relative humidity**	**Ratio of water loss rates at a given temperature**
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

d. Drug products intended for storage in a refrigerator (2.2.7.4)

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted bebw.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipment and handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

e. Drug products intended for storage in a freezer (2.2.7.5)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

f. Drug products intended for storage below -20°C (2.2.7.6)

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

8. Stability Commitment (2.2.8)

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.

- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

9. Evaluation (2.2.9)

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

10. Statements/Labeling (2.2.10)

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

GLOSSARY (3)

The following definitions are provided to facilitate interpretation of the guidance.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing: The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zones: The four zones in the world that are distinguished by their characteristic, prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany,* 28:196-202, 1985 and 29:39-47, 1986).

Commitment batches: Production batches of a drug substance or drug product for which the stability studies are initiated or completed postapproval through a commitment madein the registration application.

Container closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form: A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Formal stability studies: Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents (e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions).

Intermediate testing: Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long-term at 25°C.

Long-term testing: Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.

Mass balance: The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical error.

Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature: A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes *(J. Pharm. Sci.*, 60:927-929, 1971) can be used.

New molecular entity: An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or noncovalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For

solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is larger.

Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch: A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semipermeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification: See ICH Q6A and Q6B.

Specification, Release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification, Shelf life: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances: The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data: Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

REFERENCES (4)[3]

ICH Q1B Photostability Testing of New Drug Substances and Products

ICH Q1C Stability Testing for New Dosage Forms

ICH Q3A Impurities in New Drug Substances

ICH Q3B Impurities in New Drug Products

ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

ICH Q6B Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm

ATTACHMENT
List of Revision 2 Changes

The revisions to this *Q1A* guidance result from adoption of the ICH guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV.* The following changes were made.

1. The intermediate storage condition has been changed from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH in the following sections:

   - II.A.7.a (2.1.7.1) Drug Substance - Storage Conditions - General case
   - II.B.7.a (2.2.7.1) Drug Product - Storage Conditions - General case
   - II.B.7.c (2.2.7.3) Drug products packaged in semipermeable containers
   - Glossary (3) *Intermediate testing*

2. 30°C ± 2°C/65% RH ± 5% RH has been added as a suitable alternative long-term storage condition to 25°C ± 2°C/60% RH ± 5% in the following sections:

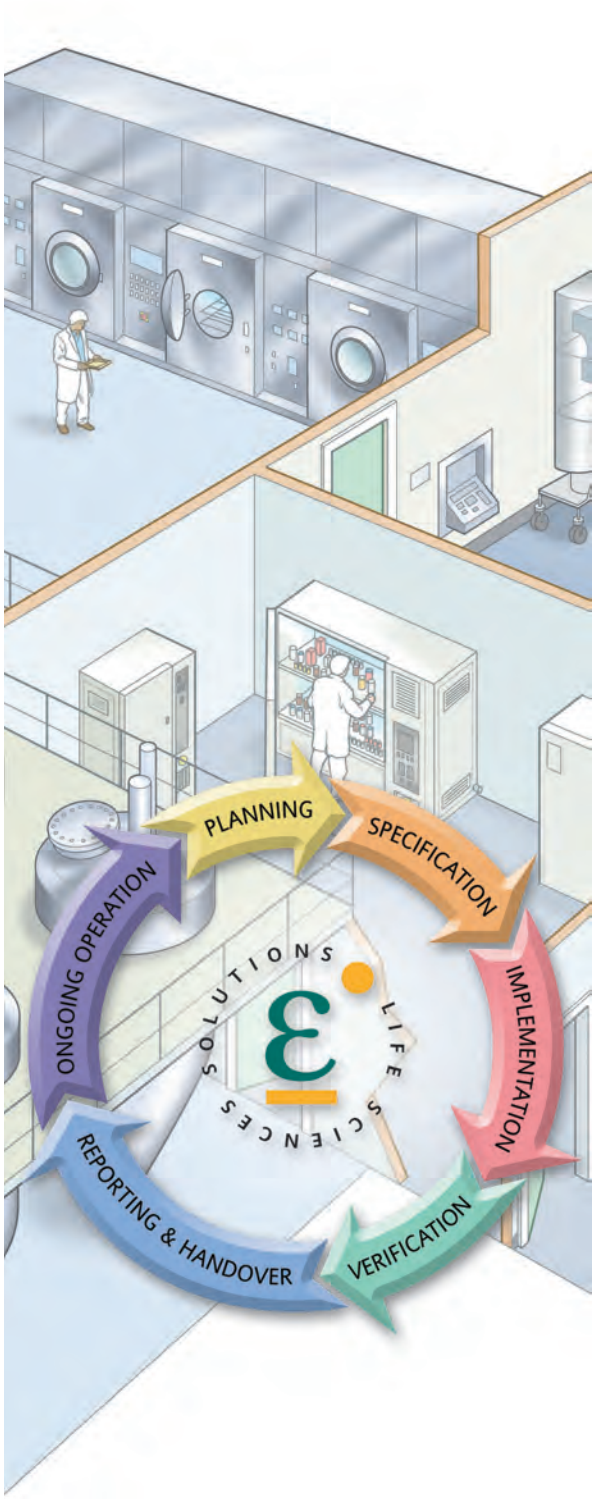
   - II.A.7.a (2.1.7.1) Drug Substance - Storage Conditions - General case
   - II.B.7.a (2.2.7.1) Drug Product - Storage Conditions - General case

3. 30°C ± 2°C/35% RH ± 5% RH has been added as a suitable alternative long-term storage condition to 25°C ± 2°C/40% RH ± 5% and the corresponding example for the ratio of water-loss rates has been included in the following section:

   - II.B.7.c (2.2.7.3) Drug products packaged in semipermeable containers

Midstream switch of the intermediate storage condition from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application.

It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65% RH ± 5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.



APPENDIX 2

Electronic Code of Federal Regulations - e-CFR

- Part 58 - Good laboratory practice for nonclinical laboratory studies
- Part 600 - Biological products: General
- Part 11 - Electronic records; Electronic signatures
- Part 210 - Current good manufacturing practice in manufacturing, processing, packaging, or holding of drugs; general
- Part 800 - General
- Part 606 - Current good manufacturing practice for blood and blood component
- Part 820 - Quality system regulations
- Part 211 - Current good manufacturing pratice for finished pharmacueticals

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Title 21: Food and Drugs

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

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Authority: 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 360, 360b–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 262, 263b–263n.

Source: 43 FR 60013, Dec. 22, 1978, unless otherwise noted.

Subpart A—General Provisions

58.1 Scope.

(a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 510, 512–516, 518–520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354–360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 64 FR 399, Jan. 5, 1999]

58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 *et seq.,* as amended (21 U.S.C. 321–392)).

(b) *Test article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act.

(c) *Control article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

(d) *Nonclinical laboratory study* means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

(e) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.35 and 570.35.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) An *investigational new drug application,* described in part 312 of this chapter.

(6) A *new drug application,* described in part 314.

(7) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(8) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in parts 109 and 509.

(9) [Reserved]

(10) A *Notice of Claimed Investigational Exemption for a New Animal Drug,* described in part 511.

(11) A *new animal drug application,* described in part 514.

(12) [Reserved]

(13) An *application for a biologics license,* described in part 601 of this chapter.

(14) An *application for an investigational device exemption,* described in part 812.

(15) An *Application for Premarket Approval of a Medical Device,* described in section 515 of the act.

(16) A *Product Development Protocol for a Medical Device,* described in section 515 of the act.

(17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in part 860.

(18) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in part 861.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in 1010.4.

(22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in 1010.5.

(23) A premarket notification for a food contact substance, described in part 170, subpart D, of this chapter.

(f) *Sponsor* means:

(1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study;

(2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

(3) A testing facility, if it both initiates and actually conducts the study.

(g) *Testing facility* means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. *Testing facility* includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. *Testing facility* encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

(h) *Person* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

(i) *Test system* means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. *Test system* also includes appropriate groups or components of the system not treated with the test or control articles.

(j) *Specimen* means any material derived from a test system for examination or analysis.

(k) *Raw data* means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. *Raw data* may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

(l) *Quality assurance unit* means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

(m) *Study director* means the individual responsible for the overall conduct of a nonclinical laboratory study.

(n) *Batch* means a specific quantity or lot of a test or control article that has been characterized according to §58.105(a).

(o) *Study initiation date* means the date the protocol is signed by the study director.

(p) *Study completion date* means the date the final report is signed by the study director.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989; 64 FR 56448, Oct. 20, 1999; 67 FR 35729, May 21, 2002]

58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

58.15 Inspection of a testing facility.

(a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.

Subpart B—Organization and Personnel

58.29 Personnel.

(a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

(b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

(c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

(e) Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

(f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

(a) Designate a study director as described in 58.33, before the study is initiated.

(b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.

(c) Assure that there is a quality assurance unit as described in 58.35.

(d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

(e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.

(f) Assure that personnel clearly understand the functions they are to perform.

(g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.33 Study director.

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall assure that:

(a) The protocol, including any change, is approved as provided by 58.120 and is followed.

(b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.

(c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.

(d) Test systems are as specified in the protocol.

(e) All applicable good laboratory practice regulations are followed.

(f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

[43 FR 60013, Dec. 22, 1978; 44 FR 17657, Mar. 23, 1979]

58.35 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(b) The quality assurance unit shall:

(1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director.

(2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible.

(3) Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.

(4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.

(6) Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.

(7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.

(c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration.

(d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart C—Facilities

58.41 General.

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

[52 FR 33780, Sept. 4, 1987]

58.43 Animal care facilities.

(a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

(b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

(d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.45 Animal supply facilities.

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.47 Facilities for handling test and control articles.

(a) As necessary to prevent contamination or mixups, there shall be separate areas for:

(1) Receipt and storage of the test and control articles.

(2) Mixing of the test and control articles with a carrier, e.g., feed.

(3) Storage of the test and control article mixtures.

(b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

58.49 Laboratory operation areas.

Separate laboratory space shall be provided, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies.

[52 FR 33780, Sept. 4, 1987]

58.51 Specimen and data storage facilities.

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

Subpart D—Equipment

58.61 Equipment design.

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

[52 FR 33780, Sept. 4, 1987]

58.63 Maintenance and calibration of equipment.

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

(b) The written standard operating procedures required under 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.

(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart E—Testing Facilities Operation

58.81 Standard operating procedures.

(a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

(b) Standard operating procedures shall be established for, but not limited to, the following:

(1) Animal room preparation.

(2) Animal care.

(3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.

(4) Test system observations.

(5) Laboratory tests.

(6) Handling of animals found moribund or dead during study.

(7) Necropsy of animals or postmortem examination of animals.

(8) Collection and identification of specimens.

(9) His athology.

(10) Data handling, storage, and retrieval.

(11) Maintenance and calibration of equipment.

(12) Transfer, proper placement, and identification of animals.

(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.

(d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

58.90 Animal care.

(a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

(b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

(e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

(f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

(h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

(i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 54 FR 15924, Apr. 20, 1989; 56 FR 32088, July 15, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart F—Test and Control Articles

58.105 Test and control article characterization.

(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

(c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

(d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by 58.195.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

58.107 Test and control article handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

(a) There is proper storage.

(b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

(c) Proper identification is maintained throughout the distribution process.

(d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

58.113 Mixtures of articles with carriers.

(a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:

(1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture.

(2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either:

(i) Before study initiation, or

(ii) Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

(b) [Reserved]

(c) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

[43 FR 60013, Dec. 22, 1978, as amended at 45 FR 24865, Apr. 11, 1980; 52 FR 33781, Sept. 4, 1987]

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

58.120 Protocol.

(a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information:

(1) A descriptive title and statement of the purpose of the study.

(2) Identification of the test and control articles by name, chemical abstract number, or code number.

(3) The name of the sponsor and the name and address of the testing facility at which the study is being conducted.

(4) The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

(5) The procedure for identification of the test system.

(6) A description of the experimental design, including the methods for the control of bias.

(7) A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(8) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.

(9) The type and frequency of tests, analyses, and measurements to be made.

(10) The records to be maintained.

(11) The date of approval of the protocol by the sponsor and the dated signature of the study director.

(12) A statement of the proposed statistical methods to be used.

(b) All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

58.130 Conduct of a nonclinical laboratory study.

(a) The nonclinical laboratory study shall be conducted in accordance with the protocol.

(b) The test systems shall be monitored in conformity with the protocol.

(c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

(d) Records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen his athologically.

(e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

Subparts H–I [Reserved]

Subpart J—Records and Reports

58.185 Reporting of nonclinical laboratory study results.

(a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following:

(1) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

(2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.

(3) Statistical methods employed for analyzing the data.

(4) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.

(5) Stability of the test and control articles under the conditions of administration.

(6) A description of the methods used.

(7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.

(8) A description of the dosage, dosage regimen, route of administration, and duration.

(9) A description of all cirmcumstances that may have affected the quality or integrity of the data.

(10) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.

(11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

(12) The signed and dated reports of each of the individual scientists or other professionals involved in the study.

(13) The locations where all specimens, raw data, and the final report are to be stored.

(14) The statement prepared and signed by the quality assurance unit as described in §58.35(b)(7).

(b) The final report shall be signed and dated by the study director.

(c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

58.190 Storage and retrieval of records and data.

(a) All raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical laboratory study shall be retained.

(b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations.

(c) An individual shall be identified as responsible for the archives.

(d) Only authorized personnel shall enter the archives.

(e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

58.195 Retention of records.

(a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter.

(b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b)(2) of this section.

(2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

(3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

(c) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, faeces, and biological fluids), samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.

(d) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by 58.35(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.

(e) Summaries of training and experience and job descriptions required to be maintained by 58.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section.

(f) Records and reports of the maintenance and calibration and inspection of equipment, as required by 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.

(g) Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.

(h) If a facility conducting nonclinical testing goes out of business, all raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The Food and Drug Administration shall be notified in writing of such a transfer.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989]

Subpart K—Disqualification of Testing Facilities

58.200 Purpose.

(a) The purposes of disqualification are:

(1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and

(2) To exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

(b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

58.202 Grounds for disqualification.

The Commissioner may disqualify a testing facility upon finding all of the following:

(a) The testing facility failed to comply with one or more of the regulations set forth in this part (or any other regulations regarding such facilities in this chapter);

(b) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and

(c) Other lesser regulatory actions (e.g., warnings or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the good laboratory practice regulations.

58.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under 58.202 which in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.

(b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.

58.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaulation of the administrative record of the disqualification proceeding, makes the findings required in 58.202, he shall issue a final order disqualifying the facility. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the testing facility of the action.

(b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in 58.202, he shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination. Upon issuing a final order the Commissioner shall notify the testing facility and provide a copy of the order.

58.210 Actions upon disqualification.

(a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

(b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit, unless the facility has been reinstated under 58.219. The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

[43 FR 60013, Dec. 22, 1978, as amended at 59 FR 13200, Mar. 21, 1994]

58.213 Public disclosure of information regarding disqualification.

(a) Upon issuance of a final order disqualifying a testing facility under 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations set forth in this part. Such notice, if given, shall include a copy of the final order issued under 58.206(a) and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified.

(b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under part 20 of this chapter.

58.215 Alternative or additional actions to disqualification.

(a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

(b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.

58.217 Suspension or termination of a testing facility by a sponsor.

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has

been submitted to any Center of the Food and Drug Administration (whether approved or not), it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

[43 FR FR 60013, Dec. 22, 1978, as amended at 50 FR 8995, Mar. 6, 1985]

58.219 Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised. A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection. If a testing facility is reinstated, the Commissioner shall so notify the testing facility and all organizations and persons who were notified, under §58.213 of the disqualification of the testing facility. A determination that a testing facility has been reinstated is disclosable to the public under part 20 of this chapter.

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Title 21: Food and Drugs

PART 600—BIOLOGICAL PRODUCTS: GENERAL

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Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25. Cross **References:** For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

600.2 Mailing addresses.

(a) *Licensed biological products regulated by the Center for Biologics Evaluation and Research (CBER)*. Unless otherwise stated in paragraphs (c) or (d) of this section, or as otherwise prescribed by FDA regulation, all submissions to CBER referenced in parts 600 through 680 of this chapter, as applicable, must be sent to: Document Control Center (HFM–99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Examples of such submissions include: Biologics license applications (BLAs) and their amendments and supplements, adverse experience reports, biological product deviation reports, fatality reports, and other correspondence. Biological products samples must not be sent to this address but must be sent to the address in paragraph (c) of this section.

(b) *Licensed biological products regulated by the Center for Drug Evaluation and Research (CDER)*. Unless otherwise stated in paragraphs (b)(1), (b)(2), (b)(3), or (c) of this section, or as otherwise prescribed by FDA regulation, all submissions to CDER referenced in parts 600, 601, and 610 of this chapter, as applicable, must be sent to: CDER Therapeutic Biological Products Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852. Examples of such submissions include: BLAs and their amendments and supplements, and other correspondence.

(1) *Biological Product Deviation Reporting (CDER)*. All biological product deviation reports required under 600.14 must be sent to: Division of Compliance Risk Management and Surveillance (HFD–330), Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(2) *Postmarketing Adverse Experience Reporting (CDER)*. All postmarketing reports required under §600.80 must be sent to: Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705–1266.

(3) *Advertising and Promotional Labeling (CDER)*. All advertising and promotional labeling supplements required under 601.12(f) of this chapter must be sent to: Division of Drug Marketing, Advertising and Communication (HFD–42), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, rm. 8B45, Rockville, MD 20857.

(c) *Samples and Protocols for licensed biological products regulated by CBER or CDER*. (1) Biological product samples and/or protocols, other than radioactive biological product samples and protocols, required under 600.13, 600.22, 601.15, 610.2, 660.6, 660.36, or 660.46 of this chapter must be sent by courier service to: Sample Custodian (ATTN: HFM–672), Food and Drug Administration, Center for Biologics Evaluation and Research, Bldg: NLRC–B, rm. 113, 5516 Nicholson Lane, Kensington, MD 20895. The protocol(s) may be placed in the box used to ship the samples to CBER. A cover letter should not be included when submitting the protocol with the sample unless it contains pertinent information affecting the release of the lot.

(2) Radioactive biological products required under 610.2 of this chapter must be sent by courier service to: Sample Custodian (ATTN: HFM–672), Food and Drug Administration, Center for Biologics Evaluation and Research, Nicholson Lane Research Center, c/o Radiation Safety Office, National Institutes of Health, 21 Wilson Dr., rm. 107, Bethesda, MD 20892–6780.

(d) *Vaccine Adverse Event Reporting System (VAERS)*. All VAERS reports as specified in 600.80(c) must be sent to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849–1100.

(e) Address information for submissions to CBER and CDER other than those listed in parts 600 through 680 of this chapter are included directly in the applicable regulations.

(f) Obtain updated mailing address information for biological products regulated by CBER at *http://www.fda.gov/cber/pubinquire.htm*, or for biological products regulated by CDER at *http://www.fda.gov/cder/biologics/default.htm*.

[70 FR 14981, Mar. 24, 2005]

600.3 Definitions.

As used in this subchapter:

(a) *Act* means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.

(c) *Commissioner of Food and Drugs* means the Commissioner of the Food and Drug Administration.

(d) *Center for Biologics Evaluation and Research* means Center for Biologics Evaluation and Research of the Food and Drug Administration.

(e) *State* means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(f) *Possession* includes among other possessions, Puerto Rico and the Virgin Islands.

(g) *Products* includes biological products and trivalent organic arsenicals.

(h) *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(i) *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) A product is deemed *applicable to the prevention, treatment, or cure of diseases or injuries of man* irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) *Proper name*, as applied to a product, means the name designated in the license for use upon each package of the product.

(l) *Dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) Expiration date means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.

(o) The word *continued* as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(q) The word *sterility* is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests prescribed in 610.12 of this chapter.

(r) *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(s) The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(t) *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; “Manufacturer” also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

(u) *Manufacture* means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(v) *Location* includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) *Establishment* has the same meaning as “facility” in section 351 of the Public Health Service Act and includes all locations.

(x) *Lot* means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(y) A *filling* refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(z) *Process* refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(aa) *Selling agent* or *distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

(ee) *Radioactive biological product* means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(ff) *Amendment* is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) *Supplement* is a request to approve a change in an approved license application.

(hh) *Distributed* means the biological product has left the control of the licensed manufacturer.

(ii) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

(jj) *Assess the effects of the change*, as used in 601.12 of this chapter, means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a product as these factors may relate to the safety or effectiveness of the product.

(kk) *Specification*, as used in 601.12 of this chapter, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

[38 FR 32048, Nov. 20, 1973, as amended at 40 FR 31313, July 25, 1975; 55 FR 11014, Mar. 26, 1990; 61 FR 24232, May 14, 1996; 62 FR 39901, July 24, 1997; 64 FR 56449, Oct. 20, 1999; 65 FR 66634, Nov. 7, 2000; 68 FR 18766, Apr. 8, 2004; 70 FR 14981, Mar. 24, 2005]

Subpart B—Establishment Standards

600.10 Personnel.

(a) [Reserved]

(b) *Personnel*. Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this subchapter to their respective functions. Personnel shall include such professionally trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) *Restrictions on personnel*—(1) *Specific duties*. Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) *Sterile operations*. Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) *Pathogenic viruses and spore-forming organisms*. Persons working with viruses pathogenic for man or with spore-forming microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) *Live vaccine work areas.* Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997; 68 FR 75119, Dec. 30, 2003]

600.11 Physical establishment, equipment, animals, and care.

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment*. Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5° C maintained for 20 minutes by saturated steam or by an attained temperature of 170° C maintained for 2 hours with dry heat. Processing and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or

otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*—(1) Work of a diagnostic nature. Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-forming pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-forming organisms for supplemental sterilization procedure control test.* Spore-forming organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: *Provided*, That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the sterility test area or areas designated for work with spore-forming organisms, (iv) each culture be labeled with the name of the microorganism and the statement "Caution: microbial spores. See directions for storage, use and disposition.", and (v) the container of each culture is designed to withstand handling without breaking.

(3) *Work with spore-forming microorganisms.* (i) Manufacturing processes using spore-forming microorganisms conducted in a multiproduct manufacturing site must be performed under appropriate controls to prevent contamination of other products and areas within the site. Prevention of spore contamination can be achieved by using a separate dedicated building or by using process containment if manufacturing is conducted in a multiproduct manufacturing building. All product and personnel movement between the area where the spore-forming microorganisms are manufactured and other manufacturing areas must be conducted under conditions that will prevent the introduction of spores into other areas of the facility.

(ii) If process containment is employed in a multiproduct manufacturing area, procedures must be in place to demonstrate adequate removal of the spore-forming microorganism(s) from the manufacturing area for subsequent manufacture of other products. These procedures must provide for adequate removal or decontamination of the spore-forming microorganisms on and within manufacturing equipment, facilities, and ancillary room items as well as the removal of disposable or product dedicated items from the manufacturing area. Environmental monitoring specific for the spore-forming microorganism(s) must be conducted in adjacent areas during manufacturing operations and in the manufacturing area after completion of cleaning and decontamination.

(4) *Live vaccine processing.* Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

(5) *Equipment and supplies—contamination.* Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing*. Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General*. No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys*. In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus*. Horses and other animals susceptible to tetanus, that are used in the processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products*. Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used, shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) *Reporting of certain diseases*. In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2).

(7) *Monkeys used previously for experimental or test purposes*. Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this subchapter, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys*. Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures*. Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) Containers and closures. All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in §610.60 et seq. of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 68 FR 75119, Dec. 30, 2003; 70 FR 14982, Mar. 24, 2005]

600.12 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: Provided, That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

600.13 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, and Source Plasma and Allergenic Products prepared to a physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in §600.2). Exceptions may be authorized by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

[41 FR 10428, Mar. 11, 1976, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

600.14 Reporting of biological product deviations by licensed manufacturers.

(a) *Who must report under this section?* (1) You, the manufacturer who holds the biological product license and who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(2) Exceptions:
(i) Persons who manufacture only in vitro diagnostic products that are not subject to licensing under section 351 of the Public Health Service Act do not report biological product deviations for those products under this section but must report in accordance with part 803 of this chapter;

(ii) Persons who manufacture blood and blood components, including licensed manufacturers, unlicensed registered blood establishments, and transfusion services, do not report biological product deviations for those products under this section but must report under 606.171 of this chapter;

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:

(A) Under 606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or

(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component, and during manufacture of the licensed biological product.

(b) *What do I report under this section?* You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications tat may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves a distributed biological product.

(c) *When do I report under this section?* You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section?* You must report on Form FDA–3486.

(e) *Where do I report under this section?* (1) For biological products regulated by the Center for Biologics Evaluation and Research (CBER), send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600) (see mailing addresses in §600.2), or an electronic filing through CBER's Web site at *http://www.fda.gov/cber/biodev/biodev.htm*.

(2) For biological products regulated by the Center for Drug Evaluation and Research (CDER), send the completed Form FDA–3486 to the Division of Compliance Risk Management and Surveillance (HFD–330) (see mailing addresses in §600.2). CDER does not currently accept electronic filings.

(3) If you make a paper filing, you should identify on the envelope that a biological product deviation report (BPDR) is enclosed.

(f) How does this regulation affect other FDA regulations? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211 and 820 of this chapter.

[65 FR 66634, Nov. 7, 2000, as amended at 70 FR 14982, Mar. 24, 2005]

600.15 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

(a) Products.

Product	Temperature
Cryoprecipitated AHF	-18 °C or colder.
Measles and Rubella Virus Vaccine Live	10 °C or colder.
Measles Live and Smallpox Vaccine	Do.
Measles, Mumps, and Rubella Virus Vaccine Live.	Do.
Measles and Mumps Virus Vaccine Live	Do.
Measles Virus Vaccine Live	Do.
Mumps Virus Vaccine Live	Do.
Fresh Frozen Plasma	-18 °C or colder.
Liquid Plasma	1 to 10 °C.
Plasma	-18 °C or colder.
Platelet Rich Plasma	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 and 24 °C, if the label indicates storage between 20 and 24 °C.

Platelets	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24°C, if the label indicates storage between 20 and 24 °C.
Poliovirus Vaccine Live Oral Trivalent	0 °C or colder.
Poliovirus Vaccine Live Oral Type I	Do.
Poliovirus Vaccine Live Oral Type II	Do.
Poliovirus Vaccine Live Oral Type III	Do.
Red Blood Cells (liquid product)	Between 1 and 10 °C.
Red Blood Cells Frozen	-65 °C or colder.
Rubella and Mumps Virus Vaccine Live	10 °C or colder.
Rubella Virus Vaccine Live	Do.
Smallpox Vaccine (Liquid Product)	0 °C or colder.
Source Plasma	-5 °C or colder.
Source Plasma Liquid	10 °C or colder.
Whole Blood	Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine	0 °C or colder.

(b) *Exemptions*. Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, approved by the Director, Center for Biologics Evaluation and Research.

[39 FR 39872, Nov. 12, 1974, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 50 FR 9000, Mar. 6, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 56449, Oct. 20, 1999]

Subpart C—Establishment Inspection

600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

[38 FR 32048, Nov. 20, 1973]

600.21 Time of inspection.

The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

[38 FR 32048, Nov. 20, 1973, as amended at 48 FR 26314, June 7, 1983; 64 FR 56449, Oct. 20, 1999]

600.22 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2), adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to 600.12,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

Subpart D—Reporting of Adverse Experiences

Source: 59 FR 54042, Oct. 27, 1994, unless otherwise noted.

600.80 Postmarketing reporting of adverse experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

Adverse experience. Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: An adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

Blood Component. As defined in 606.3(c) of this chapter.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse experience. Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.Serious adverse experience. Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse experience: Any adverse experience that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) *Review of adverse experiences.* Any person having a biologics license under 601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) *Reporting requirements*. The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products to the Center for Biologics Evaluation and Research (HFM–210), or to the Center for Drug Evaluation and Research (see mailing addresses in 600.2). Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS) (see mailing addresses in §600.2). FDA may waive the requirement for the second copy in appropriate instances.

(1)(i) *Postmarketing 15-day "Alert reports"*. The licensed manufacturer shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer.

(ii) *Postmarketing 15-day "Alert reports"—followup*. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) *Submission of reports*. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final biological product may be met by submission of all reports of serious adverse experiences to the licensed manufacturer of the final product. If a person elects to submit adverse experience reports to the licensed manufacturer of the final product rather than to FDA, the person shall submit each report to the licensed manufacturer of the final product within 5 calendar days of receipt of the report by the person, and the licensed manufacturer of the final product shall then comply with the requirements of this section. Under this circumstance, a person who elects to submit reports to the licensed manufacturer of the final product shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the licensed manufacturer of the final product; and–

(D) The name and address of the licensed manufacturer of the final product.

(iv) *Report identification*. Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report," or "15-day Alert report-followup."

(2) *Periodic adverse experience reports*. (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. Upon written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

(A) A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the licensed manufacturer's patient identification number, adverse reaction term(s), and date of submission to FDA);

(B) A form designated for Adverse Experience Reporting by FDA for each adverse experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the licensed manufacturer's patient identification number and adverse reaction term(s)); and

(C) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature shall be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph

(c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on the reporting form designated by FDA or comparable format as prescribed by paragraph (f) of this section. In cases where the licensed manufacturer believes that preparing the form designated by FDA constitutes an undue hardship, the licensed manufacturer may arrange with the Division of Biostatistics and Epidemiology (HFM–210) for an acceptable alternative reporting format.

(e) *Postmarketing studies.* (1) Licensed manufacturers are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience.

(2) The licensed manufacturer shall separate and clearly mark reports of adverse experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the licensed manufacturer.

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA for each report of an adverse experience (FDA Form 3500A, or, for vaccines, a VAERS form; foreign events including those associated with the use of vaccines, may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

(2) Each completed form should refer only to an individual patient or single attached publication.

(3) Instead of using a designated reporting form, a licensed manufacturer may use a computer-generated form or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in the form designated by FDA; and

(ii) the format is approved in advance by MEDWATCH: The FDA Medical Products Reporting Program; or, for alternatives to the VAERS Form, by the Division of Biostatistics and Epidemiology.

(4) Copies of the reporting form designated by FDA (FDA–3500A) for nonvaccine biological products may be obtained from *http://www.fda.gov/medwatch/getforms.htm*. Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1–800–822–7967.

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the biologics license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the biologics license application for the product listed first in the report.

(h) *Patient privacy.* For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public

information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, “Epidemiologic Studies and Surveillance of Disease Problems.” Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(i) *Recordkeeping*. The licensed manufacturer shall maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.

(j) *Revocation of biologics license*. If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the biologics license for such a product in accordance with the procedures of 601.5 of this chapter.

(k) *Exemptions*. Manufacturers of the following listed products are not required to submit adverse experience reports under this section:

(1) Whole blood or components of whole blood.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(l) *Disclaimer*. A report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. A licensed manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

[59 FR 54042, Oct. 27, 1994, as amended at 62 FR 34168, June 25, 1997; 62 FR 52252, Oct. 7, 1997; 63 FR 14612, Mar. 26, 1998; 64 FR 56449, Oct. 20, 1999; 70 FR 14982, Mar. 24, 2005]

600.81 Distribution reports.

The licensed manufacturer shall submit to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in 600.2), information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months. The distribution report shall consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the licensed manufacturer submit reports under this section at times other than those stated. Requests by a licensed manufacturer to submit reports at times other than those stated should be made as a request for a waiver under 600.90.

[59 FR 54042, Oct. 27, 1994, as amended at 64 FR 56449, Oct. 20, 1999; 70 FR 14983, Mar. 24, 2005]

600.90 Waivers.

(a) A licensed manufacturer may ask the Food and Drug Administration to waive under this section any requirement that applies to the licensed manufacturer under 600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:

(1) An explanation why the licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) A description of an alternative submission that satisfies the purpose of the requirement, or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) The licensed manufacturer's alternative submission satisfies the requirement, or

(3) The licensed manufacturer's submission otherwise justifies a waiver.

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Title 21: Food and Drugs

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

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Authority: 21 U.S.C. 321–393; 42 U.S.C. 262.
Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Subpart A—General Provisions

11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

(f) This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

[62 FR 13464, Mar. 20, 1997, as amended at 69 FR 71655, Dec. 9, 2004]

11.2 Implementation.

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

(1) The requirements of this part are met; and

(2) The document or parts of a document to be submitted have been identified in public docket No. 92S–0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201–903 (21 U.S.C. 321–393)).

(2) *Agency* means the Food and Drug Administration.

(3) *Biometrics* means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

(4) *Closed system* means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

(5) *Digital signature* means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

(6) *Electronic record* means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(7) *Electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(8) *Handwritten signature* means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(9) *Open system* means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B—Electronic Records

11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC–100), 5600 Fishers Lane, Rockville, MD 20857.

(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.

(2) Be used only by their genuine owners; and

(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

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Title 21: Food and Drugs

PART 210-CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

Section Contents

210.1 Status of current good manufacturing practice regulations.
210.2 Applicability of current good manufacturing practice regulations.
210.3 Definitions.

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.
Source: 43 FR 45076, Sept, 29, 1978, unless otherwise noted.

210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labelling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

[43 FR 45076, Sept, 29, 1978, as amended at 69 FR 29828, May 25, 2004]

210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

[69 FR 29828, May 25, 2004]

210.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to parts 211 through 226 of this chapter.

(1) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

(2) *Batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) *Drug product* means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients.
The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

(5) *Fiber* means any particulate contaminant with a length at least three times greater than its width.

(6) *Non-fiber-releasing filter* means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.

(7) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

(8) *Inactive ingredient* means any component other than an active ingredient.

(9) *In-process material* means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

(10) *Lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) *Lot number, control number,* or *batch number* means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.

(12) *Manufacture, processing, packing,* or *holding of a drug product* includes packaging and labelling operations, testing, and quality control of drug products.

(13) The term *medicated feed* means any Type B or Type C medicated feed as defined in 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 of this chapter.

(14) The term *medicated premix* means a Type A medicated article as defined in 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 of this chapter.

(15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) *Strength* means:

(i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) *Theoretical yield* means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) *Actual yield* means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.

(19) *Percentage of theoretical yield* means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) *Representative sample* means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) Gang-printed labelling means labelling derived from a sheet of material on which more than one item of labelling is printed.

[43 FR 45076, Sept. 29, 1978, as amended at 51 FR 7389, Mar. 3, 1986; 58 FR 41353, Aug. 3, 1993]

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Title 21: Food and Drugs

PART 800—GENERAL

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Authority: 21 U.S.C. 321, 334, 351, 352, 355, 360e, 360i, 360k, 361, 362, 371.

Subpart A [Reserved]

Subpart B—Requirements for Specific Medical Devices

800.10 Contact lens solutions; sterility.

(a)(1) Informed medical opinion is in agreement that all preparations offered or intended for ophthalmic use, including contact lens solutions, should be sterile. It is further evident that such preparations purport to be of such purity and quality as to be suitable for safe use in the eye.

(2) The Food and Drug Administration concludes that all such preparations, if they are not sterile, fall below their professed standard of purity or quality and may be unsafe. In a statement of policy issued on September 1, 1964, the Food and Drug Administration ruled that liquid preparations offered or intended for ophthalmic use that are not sterile may be regarded as adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act (the act), and, further, may be deemed misbranded within the meaning of section 502(j) of the act. By this regulation, this ruling is applicable to all preparations for ophthalmic use that are regulated as medical devices, i.e., contact lens solutions. By the regulation in 200.50 of this chapter, this ruling is applicable to ophthalmic preparations that are regulated as drugs.

(3) The containers shall be sterile at the time of filling and closing, and the container or individual carton shall be so sealed that the contents cannot be used without destroying the seal. The packaging and labelling of these solutions shall also comply with 800.12 on tamper-resistant packaging requirements.

(b) Liquid ophthalmic preparations packed in multiple-dose containers should:

(1) Contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; or

(2) Be so packaged as to volume and type of container and so labelled as to duration of use and with such necessary warnings as to afford adequate protection and minimize the hazard of injury resulting from contamination during use.

(c) Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as medical devices unless packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened and be labelled, on or within the retail package, so as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use.

[47 FR 50455, Nov. 5, 1982]

800.12 Contact lens solutions and tablets; tamper-resistant packaging.

(a) *General*. Unless contact lens solutions used, for example, to clean, disinfect, wet, lubricate, rinse, soak, or store contact lenses and salt tablets or other dosage forms to be used to make any such solutions are packaged in tamper-resistant retail packages, there is the opportunity for the malicious adulteration of these products with risks both to individuals who unknowingly purchase adulterated products and with loss of consumer confidence in the security of the packages of over-the-counter (OTC) health care products. The Food and Drug Administration has the authority and responsibility under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national standard for tamper-resistant packaging of those OTC products vulnerable to malicious adulteration that will improve the security of OTC packaging and help assure the safety and effectiveness of the products contained therein. A contact lens solution or tablet or other dosage form to be used to make such a solution for retail sale that is not packaged in a tamper-resistant package and labelled in accordance with this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) *Requirement for tamper-resistant package*. Each manufacturer and packer who packages for retail sale a product regulated as a medical device that is a solution intended for use with contact lenses, e.g., for cleaning, disinfecting, wetting, lubricating, rinsing, soaking, or storing contact lenses or tablets or other dosage forms to be used to make any such solution shall package the product in a tamper-resistant package, if this product is accessible to the public while held for sale. A tamper-resistant package is one having an indicator or barrier to entry which, if breached or missing, can reasonably

be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of substitution of a tamper-resistant feature after tampering, the indicator or barrier to entry is required to be distinctive by design or by the use of an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term “distinctive by design” means the package cannot be duplicated with commonly available material or through commonly available processes. A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(c) *Labelling*. Each retail package of a product covered by this section is required to bear a statement that is prominently placed so that consumers are alerted to the tamper-resistant feature of the package. The labelling statement is also required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labelling statement. For example, the labelling statement on a bottle with a shrink band could say “For your protection, this bottle has an imprinted seal around the neck.”

(d) *Requests for exemptions from packaging and labeling requirements*. A manufacturer or packer may request an exemption from the packaging and labelling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a “Request for Exemption from Tamper-resistant Rule.” A petition for an exemption from a requirement of this section is required to contain the same kind of information about the product as is specified for OTC drugs in 211.132(d) of this chapter. This information collection requirement has been approved by the Office of Management and Budget under number 0910–0150.

(e) *Products subject to approved premarket approval applications*. Holders of approved premarket approval applications for products subject to this section are required to submit supplements to provide for changes in packaging to comply with the requirement of paragraph (b) of this section unless these changes do not affect the composition of the container, the torque (tightness) of the container, or the composition of the closure component in contact with the contents (cap liner or innerseal) as these features are described in the approved premarket approval application. Any supplemental premarket approval application under this paragraph is required to include data sufficient to show that these changes do not adversely affect the product.

(f) *Effective date.* Each product subject to this section is required to comply with the requirements of this section on the dates listed below except to the extent that a product's manufacturer or packer has obtained an exemption from a packaging or labeling requirement:

(1) *Initial effective date for packaging requirements*. (i) The packaging requirement in paragraph (b) of this section is effective on February 7, 1983 for each contact lens solution packaged for retail sale on or after that date, except for the requirement in paragraph (b) of this section for a distinctive indicator or barrier to entry.

(ii) The packaging requirement in paragraph (b) of this section is effective on May 5, 1983 for each tablet that is to be used to make a contact lens solution and that is packaged for retail sale on or after that date.

(2) *Initial effective date for labeling requirements*. The requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design and the requirement in paragraph (c) of this section for a labeling statement are effective on May 5, 1983 for each product subject to this section packaged for retail sale on or after that date, except that the requirement for a specific label reference to any identifying characteristic is effective on February 6, 1984 for each affected product subject to this section packaged for retail sale on or after that date.

(3) *Retail level effective date.* The tamper-resistant packaging requirement of paragraph (b) of this section is effective on February 6, 1984 for each product subject to this section that is held for sale at retail level on or after that date that was packaged for retail sale before May 5, 1983. This does not include the requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design. Products packaged for retail sale after May 5, 1983, are required to be in compliance with all aspects of the regulations without regard to the retail level effective date.

[47 FR 50455, Nov. 5, 1982; 48 FR 1706, Jan. 14, 1983, as amended at 48 FR 16666, Apr. 19, 1983; 48 FR 37625, Aug. 19, 1983; 53 FR 11252, Apr. 6, 1988]

Effective Date Note: A document published at 48 FR 41579, Sept. 16, 1983, stayed the effective date of 800.12(f)(3) until further notice.

800.20 Patient examination gloves and surgeons' gloves; sample plans and test method for leakage defects; adulteration.

(a) *Purpose.* The prevalence of human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS), and its risk of transmission in the health care context, have caused the Food and Drug Administration (FDA) to look more closely at the quality control of barrier devices, such as surgeons' gloves and patient examination gloves (collectively known as medical gloves) to reduce the risk of transmission of HIV and other blood-borne infectious diseases. The Centers for Disease Control (CDC) recommend that health care workers wear medical gloves to reduce the risk of transmission of HIV and other blood-borne infectious deseases. The CDC recommends that health care workers wear medical gloves when touching blood or other body fluids, mucous membranes, or nonintact skin of all patients; when handling items or surfaces soiled with blood or other body fluids; and when performing venipuncture and other vascular access procedures. Among other things, CDC's recommendation that health care providers wear medical gloves demonstrates the proposition that devices labeled as medical gloves purport to be and are represented to be effective barriers against the transmission of blood- and fluid-borne pathogens. Therefore, FDA, through this regulation, is defining adulteration for patient examination and surgeons' gloves as a means of assuring safe and effective devices.

(1) For a description of a patient examination glove, see 880.6250. Finger cots, however, are excluded from the test method and sample plans in paragraphs (b) and (c) of this section.

(2) For a description of a surgeons' glove, see 878.4460 of this chapter.

(b) *Test method*. For the purposes of this regulation, FDA's analysis of gloves for leaks will be conducted by a water leak method, using 1,000 milliliters (mL) of water. Each medical glove will be analyzed independently. When packaged as pairs, each glove is considered separately, and both gloves will be analyzed. A defect on one of the gloves is counted as one defect; a defect in both gloves is counted as two defects. Defects are defined as leaks, tears, mold, embedded foreigh objects, etc. A leak is defined as the appearance of water on the outside of the glove. This emergence of water from the glove constitutes a watertight barrier failure. Leaks within 1 and 1/2 inches of the cuff are to be disregarded.

(1) The following materials are required for testing: A 2 3/8-inch by 15-inch (clear) plastic cylinder with a hook on one end and a mark scored 1 1/2 inches from the other end (a cylinder of another size may be used if it accommodates both cuff diameter and any water above the glove capacity); elastic strapping with velcro or other fastening material; automatic water-dispensing apparatus or manual device capable of delivering 1,000 mL of water; a stand with horizontal rod for hanging the hook end of the plastic tube. The support rod must be capable of holding the weight of the total number of gloves that will be suspended at any one time, e.g., five gloves suspended will weigh about 11 pounds.

(2) The following methodology is used: Examine the sample and identify code/ lot number, size, and brand as appropriate. Examine gloves for defects as follows: carefully remove the glove from the wrapper, box, etc., visually examining each glove for defects. Visual defects in the top 1 1/2 inches of a glove will not be counted as a defect for the purposes of this rule. Visually defective gloves do not require further testing but are to be included in the total number of defective gloves counted for the sample. Attach the glove to the plastic fill tube by bringing the cuff end to the 1 1/2-inch mark and fastening with elastic strapping to make a watertight seal. Add 1,000 mL of room temperature water (i.e., 20 °C to 30°C) into the open end of the fill tube. The water shall pass freely into the glove. (With some larger sizes of long-cuffed surgeons' gloves, the water level may reach only the base of the thumb. With some smaller gloves, the water level may extend several inches up the fill tube.)

(3) Immediately after adding the water, examine the glove for water leaks. Do not squeeze the glove; use only minimal manipulation to spread the fingers to check for leaks. Water drops may be blotted to confirm leaking. If the glove does not leak immediately, keep the glove/filling tube assembly upright and hang the assembly vertically from the horizontal rod, using the wire hook on the open end of the fill tube (do not support the filled glove while transferring). Make a second

observation for leaks 2 minutes after addition of the water to the glove. Use only minimal manipulation of the fingers to check for leaks. Record the number of defective gloves.

(c) *Sample plans*. FDA will collect samples from lots of gloves to perform the test for defects described in paragraph (b) of this section in accordance with FDA's sampling inspection plans which are based on the tables of MIL-STD-105E (the military sampling standard, "Sampling Procedures and Tables for Inspection by Attributes," May 10, 1989). Based on the acceptable quality levels found in this standard, FDA has defined adulteration as follows: 2.5 or higher for surgeons' gloves and 4.0 or higher for patient examination gloves at a general inspection level II. FDA will use single normal sampling for lots of 1,200 gloves or less and multiple normal sampling for all larger lots. For convenience, the sample plans (sample size and accept/reject numbers) are shown in the following tables:

Adulteration Level at 2.5 for Surgeons' Gloves

Lot Size	Sample	Sample Size	Number Examined	Number Defective Accept	Reject
35,001 and above	First	125	125	2	9
	Second	125	250	7	14
	Third	125	375	13	19
	Fourth	125	500	19	25
	Fifth	125	625	25	29
	Sixth	125	750	31	33
	Seventh	125	875	37	38
35,000 to 10,001	First	80	80	1	7
	Second	80	160	4	10
	Third	80	240	8	13
	Fourth	80	320	12	17
	Fifth	80	400	17	20
	Sixth	80	480	21	23
	Seventh	80	560	25	26
10,000 to 3,201	First	50	50	0	5
	Second	50	100	3	8
	Third	50	150	6	10
	Fourth	50	200	8	13
	Fifth	50	250	11	15
	Sixth	50	300	14	17
	Seventh	50	350	18	19
3,200 to 1,201	First	32	32	0	4
	Second	32	64	1	6
	Third	32	96	3	8
	Fourth	32	128	5	10
	Fifth	32	160	7	11
	Sixth	32	192	10	12
	Seventh	32	224	13	14
1,200 to 501	Single sample		80	5	6
500 to 281	Single sample		50	3	4
280 to 151	Single sample		32	2	3
150 to 51	Single sample		20	1	2
50 to 0	Single sample		5	0	1

Adulteration Level at 4.0 for Patient Examination Gloves

Lot Size	Sample	Sample Size	Number Examined	Number Defective Accept	Reject
10,001 and above	First 80	80	2	9	
	Second	80	160	7	14
	Third	80	240	13	19
	Fourth	80	320	19	25
	Fifth 80	400	25	29	
	Sixth	80	480	31	33
	Seventh	80	560	37	38
0,000 to 3,201	First 50	50	1	7	
	Second	50	100	4	10
	Third	50	150	8	13
	Fourth	50	200	12	17
	Fifth	50	250	17	20
	Sixth	50	300	21	23
	Seventh	50	350	25	26
3,200 to 1,201	First 32	32	0	5	
	Second	32	64	3	8
	Third.	32	96	6	10
	Fourth	32	128	8	13
	Fifth 32	160	11	15	
	Sixth	32	192	14	17
	Seventh	32	224	18	19
1,200 to 501	Single sample		80	7	8
500 to 281	Single sample		50	5	6
280 to 151	Single sample		32	3	4
150 to 91	Single sample		20	2	3
90 to 26	Single sample		13	1	2
25 to 0	Single sample		3	0	1

(d) Lots of gloves which are tested and rejected using the test method according to paragraph (b) of this section, are adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act, and are subject to regulatory action, such as detention of imported products and seizure of domestic products.

[55 FR 51256, Dec. 12, 1990]

Subpart C—Administrative Practices and Procedures

800.55 Administrative detention.

(a) *General.* This section sets forth the procedures for detention of medical devices intended for human use believed to be adulterated or misbranded. Administrative detention is intended to protect the public by preventing distribution or use of devices encountered during inspections that may be adulterated or misbranded, until the Food and Drug Administration (FDA) has had time to consider what action it should take concerning the devices, and to initiate legal action, if appropriate. Devices that FDA orders detained may not be used, moved, altered, or tampered with in any manner by any person during the detention period, except as authorized under paragraph (h) of this section, until FDA terminates the detention order under paragraph (j) of this section, or the detention period expires, whichever occurs first.

(b) *Criteria for ordering detention*. Administrative detention of devices may be ordered in accordance with this section when an authorized FDA representative, during an inspection under section 704 of the Federal Food, Drug, and Cosmetic Act (the act), has reason to believe that a device, as defined in section 201(h) of the act, is adulterated or misbranded.

(c) *Detention period.* The detention is to be for a reasonable period that may not exceed 20 calendar days after the detention order is issued, unless the FDA District Director in whose district the devices are located determines that a greater period is required to seize the devices, to institute injuction proceedings, or to evaluate the need for legal action, in which case the District Director may authorize detention for 10 additional calendar days. The additional 10-calendar-day detention period may be ordered at the time the detention order is issued or at any time thereafter. The entire detention period may not exceed 30 calendar days, except when the detention period is extended under paragraph (g)(6) of this section. An authorized FDA representative may, in accordance with paragraph (j) of this section, terminate a detention before the expiration of the detention period.

(d) *Issuance of detention order.* (1) The detention order shall be issued in writing, in the form of a detention notice, signed by the authorized FDA representative who has reason to believe that the devices are adulterated or misbranded, and issued to the owner, operator, or agent in charge of the place where the devices are located. If the owner or the user of the devices is different from the owner, operator, or agent in charge of the place where the devices are detained, a copy of the detention order shall be provided to the owner or user of the devices if the owner's or user's identity can be readily determined.

(2) If detention of devices in a vehicle or other carrier is ordered, a copy of the detention order shall be provided to the shipper of record and the owner of the vehicle or other carrier, if their identities can be readily determined.

(3) The detention order shall include the following information: (i) A statement that the devices identified in the order are detained for the period shown; (ii) a brief, general statement of the reasons for the detention; (iii) the location of the devices; (iv) a statement that these devices are not to be used, moved, altered, or tampered with in any manner during that period, except as permitted under paragraph (h) of this section, without the written permission of an authorized FDA representative; (v) identification of the detained devices; (vi) the detention order number; (vii) the date and hour of the detention order; (viii) the period of the detention; (ix) the text of section 304(g) of the act and paragraph (g) (1) and (2) of this section; (x) a statement that any informal hearing on an appeal of a detention order shall be conducted as a regulatory hearing under part 16 of this chapter, with certain exceptions described in paragraph (g)(3) of this section; and (xi) the location and telephone number of the FDA district office and the name of the FDA District Director.

(e) *Approval of detention order*. A detention order, before issuance, shall be approved by the FDA District Director in whose district the devices are located. If prior written approval is not feasible, prior oral approval shall be obtained and confirmed by written memorandum within FDA as soon as possible.

(f) *Labeling or marking a detained device*. An FDA representative issuing a detention order under paragraph (d) of this section shall label or mark the devices with official FDA tags that include the following information:

(1) A statement that the devices are detained by the United States Government in accordance with section 304(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 334(g)).

(2) A statement that the devices shall not be used, moved, altered, or tampered with in any manner for the period shown, without the written permission of an authorized FDA representative, except as authorized in paragraph (h) of this section.

(3) A statement that the violation of a detention order or the removal or alteration of the tag is punishable by fine or imprisonment or both (section 303 of the act, 21 U.S.C. 333).

(4) The detention order number, the date and hour of the detention order, the detention period, and the name of the FDA representative who issued the detention order.

(g) *Appeal of a detention order.* (1) A person who would be entitled to claim the devices, if seized, may appeal a detention order. Any appeal shall be submitted in writing to the FDA District Director in whose district the devices are located within 5 working days of receipt of a detention order. If the appeal includes a request for an informal hearing, as defined in section 201(y) of the act, the appellant shall request either that a hearing be held within 5 working days after the appeal is filed or that the hearing be held at a later date, which shall not be later than 20 calendar days after receipt of a detention order.

(2) The appellant of a detention order shall state the ownership or proprietary interest the appellant has in the detained devices. If the detained devices are located at a place other than an establishment owned or operated by the appellant, the appellant shall include documents showing that the appellant would have legitimate authority to claim the devices if seized.

(3) Any informal hearing on an appeal of a detention order shall be conducted as a regulatory hearing pursuant to regulation in accordance with part 16 of this chapter, except that:

(i) The detention order under paragraph (d) of this section, rather than the notice under 16.22(a) of this chapter, provides notice of opportunity for a hearing under this section and is part of the administrative record of the regulatory hearing under 16.80(a) of this chapter.

(ii) A request for a hearing under this section should be addressed to the FDA District Director.

(iii) The last sentence of 16.24(e) of this chapter, stating that a hearing may not be required to be held at a time less than 2 working days after receipt of the request for a hearing, does not apply to a hearing under this section.

(iv) Paragraph (g)(4) of this section, rather than 16.42(a) of this chapter, describes the FDA employees, i.e., regional food and drug directors, who preside at hearings under this section.

(4) The presiding officer of a regulatory hearing on an appeal of a detention order, who also shall decide the appeal, shall be a regional food and drug director (i.e., a director of an FDA regional office listed in part 5, subpart M of this chapter) who is permitted by 16.42(a) of this chapter to preside over the hearing.

(5) If the appellant requests a regulatory hearing and requests that the hearing be held within 5 working days after the appeal is filed, the presiding officer shall, within 5 working days, hold the hearing and render a decision affirming or revoking the detention.

(6) If the appellant requests a regulatory hearing and requests that the hearing be held at a date later than within 5 working days after the appeal is filed, but not later than 20 calendar days after receipt of a detention order, the presiding officer shall hold the hearing at a date agreed upon by FDA and the appellant. The presiding officer shall decide whether to affirm or revoke the detention within 5 working days after the conclusion of the hearing. The detention period extends to the date of the decision even if the 5-working-day period for making the decision extends beyond the otherwise applicable 20-calendar-day or 30-calendar-day detention period.

(7) If the appellant appeals the detention order but does not request a regulatory hearing, the presiding officer shall render a decision on the appeal affirming or revoking the detention within 5 working days after the filing of the appeal.

(8) If the presiding officer affirms a detention order, the devices continue to be detained until FDA terminates the detention under paragraph (j) of this section or the detention period expires, whichever occurs first.

(9) If the presiding officer revokes a detention order, FDA shall terminate the detention under paragraph (j) of this section.

(h)(1) *Movement of detained devices*. Except as provided in this paragraph, no person shall move detained devices within or from the place where they have been ordered detained until FDA terminates the detention under paragraph (j) of this section or the detention period expires, whichever occurs first.

(2) If detained devices are not in final form for shipment, the manufacturer may move them within the establishment where they are detained to complete the work needed to put them in final form. As soon as the devices are moved for this purpose, the individual responsible for their movement shall orally notify the FDA representative who issued the detention order, or another responsible district office official, of the movement of the devices. As soon as the devices are put in final form, they shall be segregated from other devices, and the individual responsible for their movement shall orally notify the FDA representative who issued the detention order, or another responsible district office official, of their new location. The devices put in final form shall not be moved further without FDA approval.

(3) The FDA representative who issued the detention order, or another responsible district office official, may approve, in writing, the movement of detained devices for any of the following purposes:

(i) To prevent interference with an establishment's operations or harm to the devices.

(ii) To destroy the devices.

(iii) To bring the devices into compliance.

(iv) For any other purpose that the FDA representative who issued the detention order, or other responsible district office official, believes is appropriate in the case.

(4) If an FDA representative approves the movement of detained devices under paragraph (h)(3) of this section, the detained devices shall remain segregated from other devices and the person responsible for their movement shall immediately orally notify the official who approved the movement of the devices, or another responsible FDA district office official, of the new location of the detained devices.

(5) Unless otherwise permitted by the FDA representative who is notified of, or who approves, the movement of devices under this paragraph, the required tags shall accompany the devices during and after movement and shall remain with the devices until FDA terminates the detention or the detention period expires, whichever occurs first.

(i) *Actions involving adulterated or misbranded devices.* If FDA determines that the detained devices, including any that have been put in final form, are adulterated or misbranded, or both, it may initiate legal action against the devices or the responsible individuals, or both, or request that the devices be destroyed or otherwise brought into compliance with the act under FDA's supervision.

(j) *Detention termination.* If FDA decides to terminate a detention or when the detention period expires, whichever occurs first, an FDA representative authorized to terminate a detention will issue a detention termination notice releasing the devices to any person who received the original detention order or that person's representative and will remove, or authorize in writing the removal of, the required labels or tags.

(k) *Recordkeeping requirements.* (1) After issuance of a detention order under paragraph (d) of this section, the owner, operator, or agent is charge of any factory, warehouse, other establishment, or consulting laboratory where detained devices are manufactured, processed, packed, or held shall have, or establish, and maintain adequate records relating to how the detained devices may have become adulterated or misbranded, records on any distribution of the devices before and after the detention period, records on the correlation of any in-process detained devices that are put in final form under paragraph (h) of this section to the completed devices, records of any changes in, or processing of, the devices permitted under the detention order, and records of any other movement under paragraph (h) of this section. Records required under this paragraph shall be provided to the FDA on request for review and copying. Any FDA request for access to records required under this paragraph shall be made at a reasonable time, shall state the reason or purpose for the request, and shall identify to the fullest extent practicable the information or type of information sought in the records to which access is requested.

(2) Records required under this paragraph shall be maintained for a maximum period of 2 years after the issuance of the detention order or for such other shorter period as FDA directs. When FDA terminates the detention or when the detention period expires, whichever occurs first, FDA will advise all persons required under this paragraph to keep records concerning that detention whether further recordkeeping is required for the remainder of the 2-year, or shorter, period. FDA ordinarily will not require further recordkeeping if the agency determines that the devices are not adulterated or misbranded or that recordkeeping is not necessary to protect the public health, unless the records are required under other regulations in this chapter (e.g., the good manufacturing practice regulation in part 820 of this chapter).

[44 FR 13239, Mar. 9, 1979, as amended at 49 FR 3174, Jan. 26, 1984; 69 FR 17292, Apr. 2, 2004]

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Title 21: Food and Drugs

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

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Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.
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Subpart A—General Provisions

606.3 Definitions.

As used in this part:

(a) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) *Unit* means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) *Component* means that part of a single-donor's blood separated by physical or mechanical means.

(d) *Plasma for further manufacturing* means that liquid portion of blood separated and used as material to prepare another product.

(e) *Plasmapheresis* means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.

(f) *Plateletpheresis* means the procedure in which blood is removed from a donor, a platelet concentrate is separated, and the remaining formed elements are returned to the donor along with a portion of the residual plasma.

(g) *Leukapheresis* means the procedure in which blood is removed from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(h) *Facilities* means any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components.

(i) *Processing* means any procedure employed after collection and before compatibility testing of blood and includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated recordkeeping.

(j) *Compatibility testing* means the procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient.

(k) *Distributed means:*

(1) The blood or blood components have left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or

(2) The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

(l) Control means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

[40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45370, Aug. 19, 1999; 65 FR 66635, Nov. 7, 2000; 66 FR 1835, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

Subpart B—Organization and Personnel

606.20 Personnel.

(a) [Reserved]

(b) The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components shall be adequate in number, educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(c) Persons whose presence can adversely affect the safety and purity of the products shall be excluded from areas where the collection, processing, compatibility testing, storage or distribution of blood or blood components is conducted.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997]

Subpart C—Plant and Facilities

606.40 Facilities.

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Private and accurate examinations of individuals to determine their suitability as blood donors.

(2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood collection.

(3) The storage of blood or blood components pending completion of tests.

(4) The quarantine storage of blood or blood components in a designated location pending repetition of those tests that initially gave questionable serological results.

(5) The storage of finished products prior to distribution.

(6) The quarantine storage, handling and disposition of products and reagents not suitable for use.

(7) The orderly collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) The adequate and proper performance of all steps in plasmapheresis, plateletpheresis and leukapheresis procedures.

(9) The orderly conduction of all packaging, labelling and other finishing operations.

(b) Provide adequate lighting, ventilation and screening of open windows and doors.

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(d) Provide for safe and sanitary disposal for the following:

(1) Trash and items used during the collection, processing and compatibility testing of blood and blood components.

(2) Blood and blood components not suitable for use or distribution.

Subpart D—Equipment

606.60 Equipment.

(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of Calibration
Temperature recorder	Compare against thermometer.	Daily	As necessary.
Refrigerated centrifug	Observe speed and temperature.	Each day of use	Do.
Hematocrit centrifuge			Standardize before initial use, after repairs or adjustments, and annually. Timer every 3 mo.
General lab centrifuge			Tachometer every 6 mo.
Automated blood-typing machine....	Observe controls for correct results.	Each day of use.....	
Hemoglobinometer	Standardize against cyanmethemoglobin standard.	do	
Refractometer	Standardize against distilled water.	do	
Blood container scale	Standardize agains container of known weight.	do	As necessary.
Water bath	Observe temperature	do	Do.
Rh view box	do	do	Do.
Autoclave	do	Each time of use	Do.
Serologic rotators	Observe controls for correct results.	Each day of use	Speed as necessary.
Laboratory thermometers			Before initial use.
Electronic thermometers			Monthly.

Equipment	Performance check	Frequency	Frequency of Calibration
Vacuum blood agitator	Observe weight of the first container of blood filled for correct results.	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments.

(c) Equipment employed in the sterilization of materials used in blood collection or for disposition of contaminated products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 °C (251 °F) maintained for 20 minutes by saturated steam or by an attained temperature of 170 °C (338 °F) maintained for 2 hours with dry heat.

[40 FR 53532, Nov. 18, 1975; 40 FR 55849, Dec. 2, 1975, as amended at 45 FR 9261, Feb. 12, 1980; 57 FR 11263, Apr. 2, 1992; 57 FR 12862, Apr. 13, 1992]

606.65 Supplies and reagents.

All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be stored in a safe, sanitary and orderly manner.

(a) All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(b) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

(c) Representative samples of each lot of the following reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required:

Reagent or solution	Frequency of testing
Anti-human globulin	Each day of use.
Blood grouping reagents	Do.
Lectins	Do.
Antibody screening and reverse grouping cells.	Do.
Hepatitis test reagents	Each run.
Syphilis serology reagents	Do.
Enzymes	Each day of use.

(d) Supplies and reagents that do not bear an expiration date shall be stored in such a manner that the oldest is used first.

(e) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(f) Items that are required to be sterile and come into contact with blood should be disposable whenever possible.

[40 FR 53532, Nov. 18, 1975, as amended at 59 FR 23636, May 6, 1994]

Subpart E [Reserved]

Subpart F—Production and Process Controls

606.100 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures shall comply with published additional standards in part 640 of this chapter for the products being processed; except that, references in part 640 relating to licenses, licensed establishments and submission of material or data to or approval by the Director, Center for Biologics Evaluation and Research, are not applicable to establishments not subject to licensure under section 351 of the Public Health Service Act.

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

(1) Criteria used to determine donor suitability, including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating the product(s) to the donor.

(5) Blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood removed from the donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests and repeat tests performed on blood and blood components during manufacturing.

(8) Pretransfusion testing, where applicable, including precautions to be taken to identify accurately the recipient blood samples and crossmatched donor units.

(9) Procedures for investigating adverse donor and recipient reactions.

(10) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents as prescribed in 600.15 and 610.53 of this chapter.

(11) Length of expiration dates, if any, assigned for all final products as prescribed in 610.53 of this chapter.

(12) Criteria for determining whether returned blood is suitable for reissue.

(13) Procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(14) Quality control procedures for supplies and reagents employed in blood collection, processing and pretransfusion testing.

(15) Schedules and procedures for equipment maintenance and calibration.

(16) Labelling procedures, including safeguards to avoid labelling mixups.

(17) Procedures of plasmapheresis, plateletpheresis, and leukapheresis, if performed, including precautions to be taken to ensure reinfusion of a donor's own cells.

(18) Procedures for preparing recovered plasma, if performed, including details of separation, pooling, labelling, storage, and distribution.

(19) Procedures in accordance with 610.46 of this chapter to look at prior donations of Whole Blood, blood components, Source Plasma and Source Leukocytes from a donor who has donated blood and subsequently tests repeatedly reactive for antibody to human immunodeficiency virus (HIV) or otherwise is determined to be unsuitable when tested in accordance with 610.45 of this chapter. Procedures to quarantine in-house Whole Blood, blood components, Source Plasma and Source Leukocytes intended for further manufacture into injectable products that were obtained from such donors; procedures to notify consignees regarding the need to quarantine such products; procedures to determine the suitability for release of such products from quarantine; procedures to notify consignees of Whole Blood, blood components, Source Plasma and Source Leukocytes from such donors of the results of the antibody testing of such donors; and procedures in accordance with 610.47 of this chapter to notify attending physicians so that transfusion recipients are informed that they may have received Whole Blood and, blood components at increased risk for transmitting human immunodeficiency virus.

(20) Procedures for donor deferral as prescribed in 610.41 of this chapter; and procedures for donor notification and autologous donor referring physician notification, including procedures for the appropriate follow up if the initial attempt at notification fails, as prescribed in 630.6 of this chapter.

(c) All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing. A thorough investigation, including the conclusions and follow up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 47422, Sept. 9, 1996; 64 FR 45370, Aug. 19, 1999; 66 FR 31176, June 11, 2001]

606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

(a) The use of plateletpheresis and leukapheresis procedures to obtain a product for a specific recipient may be at variance with the additional standards for specific products prescribed in this part provided that: (1) A physician has determined that the recipient must be transfused with th leukocytes or platelets from a specific donor, and (2) the procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor, and the physician has certified in writing that the donor's health permits plateletpheresis or leukapheresis.

(b) Plasmapheresis of donors who do not meet the donor requirements of 640.63, 640.64 and 640.65 of this chapter for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart G—Finished Product Control

606.120 Labelling, general requirements.

(a) Labelling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mixups.

(b) The labelling operation shall include the following labelling controls:

(1) Labels shall be held upon receipt, pending review and proofing against an approved final copy, to ensure accuracy regarding identity, content, and conformity with the approved copy.

(2) Each type of label representing different products shall be stored and maintained in a manner to prevent mixups, and stocks of obsolete labels shall be destroyed.

(3) All necessary checks in labelling procedures shall be utilized to prevent errors in translating test results to container labels.

(c) All labelling shall be clear and legible.

[50 FR 35469, Aug. 30, 1985]

606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments.

(b) The label provided by the collecting facility and the initial processing facility shall not be removed, altered, or obscured, except that the label may be altered to indicate the proper name and other information required to identify accurately the contents of a container after blood components have been prepared.

(c) The container label shall include the following information, as well as other specialized information as required in this section for specific products:

(1) The proper name of the product in a prominent position, and modifier(s), if appropriate.

(2) The name, address, registration number, and, if a licensed product, the license number of each manufacturer.

(3) The donor, pool, or lot number relating the unit to the donor.

(4) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, the hour of expiration.

(5) If the product is intended for transfusion, the appropriate donor classification statement, i.e., “paid donor” or “volunteer donor”, in no less prominence than the proper name of the product.

(i) A paid donor is a person who receives monetary payment for a blood donation.

(ii) A volunteer donor is a person who does not receive monetary payment for a blood donation.

(iii) Benefits, such as time off from work, membership in blood assurance programs, and cancellation of nonreplacement fees that are not readily convertible to cash, do not constitute monetary payment within the meaning of this paragraph.

(6) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within ±10 percent; or optionally for Platelets, the volume range within reasonable limits.

(7) The recommended storage temperature (in degrees Celsius).

(8) If the product is intended for transfusion, the statements:

(i) “Rx only.”

(ii) “See circular of information for indications, contraindications, cautions, and methods of infusion.”

(iii) “Properly identify intended recipient.”

(9) The statement: “This product may transmit infectious agents.”

(10) Where applicable, the name and volume of source material.

(11) The statement: “Caution: For Manufacturing Use Only”, when applicable.

(12) If the product is intended for transfusion, the ABO and Rh groups of the donor shall be designated conspicuously. For Cryoprecipitated AHF, the Rh group may be omitted. The Rh group shall be designated as follows:

(i) If the test using Anti-D Blood Grouping Reagent is positive, the product shall be labelled: “Rh positive.”

(ii) If the test using Anti-D Blood Grouping Reagent is negative but the test for Du is positive, the product shall be labelled: “Rh positive.”

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for Du is negative, the product shall be labelled: “Rh negative.”

(13) The container label must bear encoded information in a format that is machine-readable and approved for use by the Director, Center for Biologics Evaluation and Research.

(i) *Who is subject to this machine-readable requirement?* All blood establishments that manufacture, process, repack, or relabel blood or blood components intended for transfusion and regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(ii) *What blood products are subject to this machine-readable requirement?*
All blood and blood components intended for transfusion are subject to the machine-readable information label requirement in this section.

(iii) *What information must be machine-readable?* Each label must have machine-readable information that contains, at a minimum:

(A) A unique facility identifier;

(B) Lot number relating to the donor;

(C) Product code; and

(D) ABO and Rh of the donor.

(iv) *How must the machine-readable information appear?* The machine-readable information must:

(A) Be unique to the blood or blood component;

(B) Be surrounded by sufficient blank space so that the machine-readable information can be scanned correctly; and

(C) Remain intact under normal conditions of use.

(v) *Where does the machine-readable information go?* The machine-readable information must appear on the label of any blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

(d) Except for recovered plasma intended for manufacturing use or as otherwise approved by the Director, Center for Biologics Evaluation and Research, the paper of the container label shall be white and print shall be solid black, with the following additional exceptions:

(1) The Rh blood group shall be printed as follows:

(i) Rh positive: Use black print on white background.

(ii) Rh negative: Use white print on black background.

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement "properly identify intended recipient" shall be printed in solid red or in solid black.

(3) The following color scheme may be used optionally for differentiating ABO Blood groups:

Blood group	Color of label paper
O	Blue
A	Yellow
B	Pink
AB	White

(4) Ink colors used for the optional color coding system described in paragraph (d)(3) of this section shall be a visual match to specific color samples designated by the Director, Center for Biologics Evaluation and Research.

(5) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color coded using the colors recommended in the guideline (see paragraph (a) of this section), or colors otherwise approved for use by the Director, Center for Biologics Evaluation and Research.

(e) Container label requirements for particular products or groups of products.

(1) Whole Blood labels shall include:

(i) The volume of anticoagulant.

(ii) The name of the applicable anticoagulant immediately preceding and of no less prominence than the proper name approved for use by the Director, Center for Biologics Evaluation and Research.

(iii) If tests for unexpected antibodies are positive, blood intended for transfusion shall be labelled: "Contains (*name of antibody*)."

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, red blood cell labels shall include:

(i) The volume and kind of Whole Blood, including the type of anticoagulant, from which the product was prepared.

(ii) If tests for unexpected antibodies are positive and the product is intended for transfusion, the statement: "Contains (*name of antibody*)."

(3) Labels for products with a dating period of 72 hours or less, including any product prepared in a system that may compromise sterility, shall bear the hour of expiration.

(4) If tests for unexpected antibodies are positive, Plasma intended for transfusion shall be labelled: “Contains (*name of antibody*).”

(5) Recovered plasma labels shall include:

(i) In lieu of an expiration date, the date of collection of the oldest material in the container.

(ii) The statement as applicable: “Caution: For Manufacturing Use Only”; or “Caution: For Use in Manufacturing Noninjectable Products Only.” If the recovered plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under 10.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under 610.40 of this chapter, the recovered plasma must be labelled as required under 610.40(h)(2)(ii)(E) of this chapter.

(iii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: “Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act.”

(f) Blood and blood components determined to be unsuitable for transfusion shall be prominently labelled: “NOT FOR TRANSFUSION”, and the label shall state the reason the unit is considered unsuitable. The provision does not apply to recovered plasma labelled according to paragraph (e)(5) of this section.

(g) [Reserved]

(h) The following additional information shall appear on the label for blood or blood components shipped in an emergency, prior to completion of required tests, in accordance with 640.2(f) of this chapter:

(1) The statement: “FOR EMERGENCY USE ONLY BY _____.”

(2) Results of any tests prescribed under 610.40, and 640.5 (a), (b), or

(c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under 610.40, and 640.5 (a), (b), or (c) of this chapter and not completed before shipment.

(i) The following additional information shall appear on the label for Whole Blood or Red Blood Cells intended for autologous infusion:

(1) Information adequately identifying the patient, e.g., name, blood group, hospital, and identification number.

(2) Date of donation.

(3) The statement: “FOR AUTOLOGOUS USE ONLY.”

(4) In place of the blood group label, each container of blood intended for autologous use and obtained from a donor who fails to meet any of the donor suitability requirements under 640.3 of this chapter or who is reactive in the hepatitis tests prescribed under 610.40 of this chapter shall be prominently and permanently labelled: “FOR AUTOLOGOUS USE ONLY.”

(5) Units of blood originally intended for autologous use, except those labelled as prescribed under paragraph (i)(4) of this section, may be issued for homologous transfusion provided the container label complies with all applicable provisions of paragraphs (b) through (e) of this section. In such case, the special label required under paragraph (i) (1), (2), and (3) of this section shall be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraph (e) (1)(iii), (2)(ii), and (4), (h), or (i)(1), (2), and (3) of this section.

[50 FR 35469, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 55 FR 11014, Mar. 26, 1990; 57 FR 10814, Mar. 31, 1992; 59 FR 23636, May 6, 1994; 63 FR 16685, Apr. 6, 1998; 64 FR 45371, Aug. 19, 1999; 66 FR 31162, June 11, 2001; 67 FR 4907, Feb. 1, 2002; 69 FR 9171, Feb. 26, 2004; 70 FR 14984, Mar. 24, 2005]

606.122 Instruction circular.

An instruction circular shall be available for distribution if the product is intended for transfusion. The instruction circular shall provide adequate directions for use, including the following information:

(a) Instructions to mix the product before use.

(b) Instructions to use a filter in the administration equipment.

(c) The statement “Do Not Add Medications” or an explanation concerning allowable additives.

(d) A description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product is prepared.

(e) Statements that the product was prepared from blood that was negative when tested for antibody to Human Immunodeficiency Virus (HIV) and nonreactive for hepatitis B surface antigen by FDA required tests and nonreactive when tested for syphilis by a serologic test for syphilis (STS).

(f) The statements: “Warning. The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard.”

(g) The names of cryoprotective agents and other additives that may still be present in the product.

(h) The names and results of all tests performed when necessary for safe and effective use.

(i) The use of the product, indications, contradications, side effects and hazards, dosage and administration recommendations.

(j) [Reserved]

(k) For Red Blood Cells, the instruction circular shall contain:

(1) Instructions to administer a suitable plasma volume expander if Red Blood Cells are substituted when Whole Blood is the indicated product.

(2) A warning not to add Lactated Ringer's Injection U.S.P. solution to Red Blood Cell products.

(l) For Platelets, the instruction circular shall contain:

(1) The approximate volume of plasma from which a sample unit of Platelets is prepared.

(2) Instructions to begin administration as soon as possible, but not more than 4 hours after entering the container.

(m) For Plasma, the instruction circular shall contain:

(1) A warning against further processing of the frozen product if there is evidence of breakage or thawing.

(2) Instructions to thaw the frozen product at a temperature between 30 and 37 °C.

(3) When applicable, instructions to begin administration of the product within 6 hours after thawing.

(4) Instructions to administer to ABO-group-compatible recipients.

(5) A statement that this product has the same hepatitis risk as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.

(n) For Cryoprecipitated AHF, the instruction circular shall contain:

(1) A statement that the average potency is 80 or more International Units of antihemophilic factor.

(2) The statement: “Usually contains at least 150 milligrams of fibrinogen”; or, alternatively, the average fibrinogen level determined by assay of representative units.

(3) A warning against further processing of the product if there is evidence of breakage or thawing.

(4) Instructions to thaw the product for no more than 15 minutes at a temperature of between 30 and 37 °C.

(5) Instructions to store at room temperature after thawing and to begin administration as soon as possible but no more than 4 hours after entering the container or after pooling and within 6 hours after thawing.

(6) A statement that 0.9 percent Sodium Chloride Injection U.S.P. is the preferred diluent.

(7) Adequate instructions for pooling to ensure complete removal of all concentrated material from each container.

(8) The statement: “Good patient management requires monitoring treatment responses to Cryoprecipitated AHF transfusions with periodic plasma factor VIII or fibrinogen assays in hemophilia A and hypofibrinogenemic recipients, respectively.”

[50 FR 35470, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 64 FR 45371, Aug. 19, 1999]

Subpart H—Laboratory Controls

606.140 Laboratory controls.

Laboratory control procedures shall include:

(a) The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective.

(b) Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.

(c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor, or to the specific recipient, where applicable.

606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

(a) A method of collecting and identifying the blood samples of recipients to ensure positive identification.

(b) The use of fresh recipient serum or plasma samples less than 3 days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.

(c) Procedures to demonstrate incompatibility between the donor's cell type and the recipient's serum or plasma type.

(d) A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and haemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate.

(e) Procedures to expedite transfusion in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by a physician.

[40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45371, Aug. 19, 1999; 66 FR 1835, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

Subpart I—Records and Reports

606.160 Records.

(a)(1) Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

(2) Appropriate records shall be available from which to determine lot numbers of supplies and reagents used for specific lots or units of the final product.

(b) Records shall be maintained that include, but are not limited to, the following when applicable:

(1) Donor records:

(i) Donor selection, including medical interview and examination and where applicable, informed consent.

(ii) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

(iii) Donor adverse reaction complaints and reports, including results of all investigations and follow up.

(iv) Therapeutic bleedings, including signed requests from attending physicians, the donor's disease and disposition of units.

(v) Immunization, including informed consent, identification of the antigen, dosage and route of administration.

(vi) Blood collection, including identification of the phlebotomist.

(vii) Records to relate the donor with the unit number of each previous donation from that donor.

(viii) Records of quarantine, notification, testing, and disposition performed pursuant to 610.46 and 610.47 of this chapter.

(ix) Records of notification of donors deferred or determined not to be suitable for donation, including appropriate follow up if the initial attempt at notification fails, performed under 630.6 of this chapter.

(x) The donor's address provided at the time of donation where the donor may be contacted within 8 weeks after donation.

(xi) Records of notification of the referring physician of a deferred autologous donor, including appropriate follow up if the initial notification attempt fails, performed under §630.6 of this chapter.

(2) Processing records:

(i) Blood processing, including results and interpretation of all tests and retests.

(ii) Component preparation, including all relevant dates and times.

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labelling, including initials of the person(s) performing the procedure.

(3) Storage and distribution records:

(i) Distribution and disposition, as appropriate, of blood and blood products.

(ii) Visual inspection of whole blood and red blood cells during storage and immediately before distribution.

(iii) Storage temperature, including initialed temperature recorder charts.

(iv) Reissue, including records of proper temperature maintenance.

(v) Emergency release of blood, including signature of requesting physician obtained before or after release.

(4) Compatibility test records:

(i) Results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification.

(ii) Results of confirmatory testing.

(5) Quality control records:

(i) Calibration and standardization of equipment.

(ii) Performance checks of equipment and reagents.

(iii) Periodic check on sterile technique.

(iv) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

(v) Proficiency test results.

(6) Transfusion reaction reports and complaints, including records of investigations and followup.

(7) General records:

(i) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.

(ii) Responsible personnel.

(iii) Biological product deviations.

(iv) Maintenance records for equipment and general physical plant.

(v) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

(vi) Disposition of rejected supplies and reagents used in the collection, processing and compatibility testing of blood and blood components.

(c) A donor number shall be assigned to each accepted donor, which relates the unit of blood collected to that donor, to his medical record, to any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(d) Records shall be retained for such interval beyond the expiration date for the blood or blood component as necessary to facilitate the reporting of any unfavorable clinical reactions. The retention period shall be no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date for the individual product, whichever is a later date. When there is no expiration date, records shall be retained indefinitely.

(e) A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

[40 FR 53532, Nov. 18, 1975, as amended at 61 FR 47422, Sept. 9, 1996; 64 FR 45371, Aug. 19, 1999; 65 FR 66635, Nov. 7, 2000; 66 FR 31176, June 11, 2001]

606.165 Distribution and receipt; procedures and records.

(a) Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary.

(b) Distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

(c) Receipt records shall contain the name and address of the collecting facility, date received, donor or lot number assigned by the collecting facility and the date of expiration or the date of collection, whichever is applicable.

606.170 Adverse reaction file.

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions, including conclusions and follow up, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 50 FR 35471, Aug. 30, 1985; 55 FR 11014, Mar. 26, 1990; 64 FR 45371, Aug. 19, 1999; 67 FR 9586, Mar. 4, 2002]

606.171 Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishments, and transfusion services.

(a) Who must report under this section? You, a licensed manufacturer of blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(b) What do I report under this section? You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labelling, or storage, or with the holding or distribution, of both licensed and unlicensed blood or blood components, including Source Plasma, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves distributed blood or blood components.

(c) When do I report under this section? You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) How do I report under this section? You must report on Form FDA–3486.

(e) Where do I report under this section? You must send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600)(see mailing addresses in 600.2 of this chapter) by either a paper or electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or

(2) If you make an electronic filing, you may submit the completed Form FDA–3486 electronically through CBER's website at *www.fda.gov/cber*.

(f) How does this regulation affect other FDA regulations? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211, 606, and 820 of this chapter.

[65 FR 66635, Nov. 7, 2000, as amended at 70 FR 14984, Mar. 24, 2005]

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Title 21: Food and Drugs

PART 820-QUALITY SYSTEM REGULATION

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Subpart A-General Provisions

820.1 Scope.

(a) *Applicability*. (1) Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labelling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applicable to manufacturers of finished medical devices. If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged. With respect to class I devices, design controls apply only to those devices listed in 820.30(a)(2). This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance. Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter. Manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are medical devices (subject to premarket review or notification, or exempt from notification, under an application submitted under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act) are subject to this part and are also subject to the donor-eligibility procedures set forth in part 1271 subpart C of this chapter and applicable current good tissue practice procedures in part 1271 subpart D of this chapter. In the event of a conflict between applicable regulations in part 1271 and in other parts of this chapter, the regulation specifically applicable to the device in question shall supersede the more general.

(2) The provisions of this part shall be applicable to any finished device as defined in this part, intended for human use, that is manufactured, imported, or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(3) In this regulation the term "where appropriate" is used several times.
When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless the manufacturer can document justification otherwise. A requirement is "appropriate" if nonimplementation could reasonably be expected to result in the product not meeting its specified requirements or the manufacturer not being able to carry out any necessary corrective action.

(b) The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other generally applicable requirements.

(c) *Authority*. Part 820 is established and issued under authority of sections 501, 502, 510, 513, 514, 515, 518, 519, 520, 522, 701, 704, 801, 803 of the act (21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383). The failure to comply with any applicable provision in this part renders a device adulterated under section 501(h) of the act. Such a device, as well as any person responsible for the failure to comply, is subject to regulatory action.

(d) *Foreign manufacturers*. If a manufacturer who offers devices for import into the United States refuses to permit or allow the completion of a Food and Drug Administration (FDA) inspection of the foreign facility for the purpose of determining compliance with this part, it shall appear for purposes of section 801(a) of the act, that the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labelling, storage, installation, or servicing of any devices produced at such facility that are offered for import into the United States do not conform to the requirements of section 520(f) of the act and this part and that the devices manufactured at that facility are adulterated under section 501(h) of the act.

(e) *Exemptions or variances*. (1) Any person who wishes to petition for an exemption or variance from any device quality system requirement is subject to the requirements of section 520(f)(2) of the act. Petitions for an exemption or variance shall be submitted according to the procedures set forth in §10.30 of this chapter, the FDA's administrative procedures. Guidance is available from the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance (HFZ-220), 1350 Piccard Dr., Rockville, MD 20850, U.S.A., telephone 1-800-638-2041 or 1-301-443-6597, FAX 301-443-8818.

(2) FDA may initiate and grant a variance from any device quality system requirement when the agency determines that such variance is in the best interest of the public health. Such variance will remain in effect only so long as there remains a public health need for the device and the device would not likely be made sufficiently available without the variance.

[61 FR 52654, Oct. 7, 1996, as amended at 65 FR 17136, Mar. 31, 2000; 65 FR 66636, Nov. 7, 2000; 69 FR 29829, May 25, 2005]

820.3 Definitions.

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-903, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-394)). All definitions in section 201 of the act shall apply to the regulations in this part.

(b) *Complaint* means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

(c) *Component* means any raw material, substance, piece, part, software, firmware, labelling, or assembly which is intended to be included as part of the finished, packaged, and labelled device.

(d) *Control number* means any distinctive symbols, such as a distinctive combination of letters or numbers, or both, from which the history of the manufacturing, packaging, labelling, and distribution of a unit, lot, or batch of finished devices can be determined.

(e) *Design history file (DHF)* means a compilation of records which describes the design history of a finished device.

(f) *Design input* means the physical and performance requirements of a device that are used as a basis for device design.

(g) *Design output* means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labelling, and the device master record.

(h) *Design review* means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

(i) *Device history record (DHR)* means a compilation of records containing the production history of a finished device.

(j) *Device master record (DMR)* means a compilation of records containing the procedures and specifications for a finished device.

(k) *Establish* means define, document (in writing or electronically), and implement.

(l) *Finished device* means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labelled, or sterilized.

(m) *Lot or batch* means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits.

(n) *Management with executive responsibility* means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

(o) *Manufacturer* means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.

(p) *Manufacturing material* means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a by product constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.

(q) *Nonconformity* means the nonfulfillment of a specified requirement.

(r) *Product* means components, manufacturing materials, in- process devices, finished devices, and returned devices.

(s) *Quality* means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

(t) *Quality audit* means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

(u) *Quality policy* means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

(v) *Quality system* means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

(w) *Remanufacturer* means any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

(x) *Rework* means action taken on a nonconforming product so that it will fulfil the specified DMR requirements before it is released for distribution.

(y) *Specification* means any requirement with which a product, process, service, or other activity must conform.

(z) *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

(1) *Process validation* means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

(2) *Design validation* means establishing by objective evidence that device specifications conform with user needs and intended use(s).

(aa) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

820.5 Quality system.

Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.

Subpart B-Quality System Requirements

820.20 Management responsibility.

(a) *Quality policy*. Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

(b) *Organization*. Each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements of this part.

(1) *Responsibility and authority*. Each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks.

(2) *Resources*. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including internal quality audits, to meet the requirements of this part.

(3) *Management representative*. Management with executive responsibility shall appoint, and document such appointment of, a member of management who, irrespective of other responsibilities, shall have established authority over and responsibility for:

(i) Ensuring that quality system requirements are effectively established and effectively maintained in accordance with this part; and

(ii) Reporting on the performance of the quality system to management with executive responsibility for review.

(c) *Management review*. Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented.

(d) *Quality planning*. Each manufacturer shall establish a quality plan which defines the quality practices, resources, and activities relevant to devices that are designed and manufactured. The manufacturer shall establish how the requirements for quality will be met.

(e) *Quality system procedures*. Each manufacturer shall establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system shall be established where appropriate.

820.22 Quality audit.

Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited. Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.

820.25 Personnel.

(a) *General*. Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.

(b) *Training*. Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

(1) As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs.

(2) Personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

Subpart C-Design Controls

820.30 Design controls.

(a) *General*. (1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

(2) The following class I devices are subject to design controls:

(i) Devices automated with computer software; and

(ii) The devices listed in the following chart.

Section	Device
868.6810	Catheter, Tracheobronchial Suction.
878.4460	Glove, Surgeon's.
880.6760	Restraint, Protective.
892.5650	System, Applicator, Radionuclide, Manual.
892.5740	Source, Radionuclide Teletherapy.

(b) *Design and development planning*. Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and approved as design and development evolves.

(c) *Design input*. Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

(d) *Design output*. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

(e) *Design review*. Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file (the DHF).

(f) *Design verification*. Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

(g) *Design validation.* Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

(h) *Design transfer.* Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications.

(i) *Design changes.* Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

(j) *Design history file.* Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this

Subpart D-Document Controls

820.40 Document controls.

Each manufacturer shall establish and maintain procedures to control all documents that are required by this part. The procedures shall provide for the following:

(a) *Document approval and distribution.* Each manufacturer shall designate an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part. The approval, including the date and signature of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use.

(b) *Document changes.* Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.

Subpart E-Purchasing Controls

820.50 Purchasing controls.

Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

(a) *Evaluation of suppliers, contractors, and consultants*. Each manufacturer shall establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants. Each manufacturer shall:

(1) Evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be documented.

(2) Define the type and extent of control to be exercised over the product, services, suppliers, contractors, and consultants, based on the evaluation results.

(3) Establish and maintain records of acceptable suppliers, contractors, and consultants.

(b) *Purchasing data*. Each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Purchasing documents shall include, where possible, an agreement that the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device. Purchasing data shall be approved in accordance with 820.40.

Subpart F-Identification and Traceability

820.60 Identification.

Each manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mix ups.

820.65 Traceability.

Each manufacturer of a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and where appropriate components. The procedures shall facilitate corrective action. Such identification shall be documented in the DHR.

Subpart G-Production and Process Controls

820.70 Production and process controls.

(a) *General.* Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications. Where process controls are needed they shall include:

(1) Documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;

(2) Monitoring and control of process parameters and component and device characteristics during production;

(3) Compliance with specified reference standards or codes;

(4) The approval of processes and process equipment; and

(5) Criteria for workmanship which shall be expressed in documented standards or by means of identified and approved representative samples.

(b) *Production and process changes.* Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with 820.40.

(c) *Environmental control.* Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented and reviewed.

(d) *Personnel.* Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturer shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

(e) *Contamination control.* Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

(f) *Buildings.* Buildings shall be of suitable design and contain sufficient space to perform necessary operations, prevent mix ups, and assure orderly handling.

(g) *Equipment.* Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.

(1) *Maintenance schedule.* Each manufacturer shall establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented.

(2) *Inspection.* Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented.

(3) *Adjustment*. Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments.

(h) *Manufacturing material*. Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented.

(i) *Automated processes*. When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

820.72 Inspection, measuring, and test equipment.

(a) *Control of inspection, measuring, and test equipment*. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

(b) *Calibration*. Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to re-establish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.

(1) *Calibration standards*. Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

(2) *Calibration records*. The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

820.75 Process validation.

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

(b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

(1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.

(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

Subpart H-Acceptance Activities

820.80 Receiving, in-process, and finished device acceptance.

(a) *General*. Each manufacturer shall establish and maintain procedures for acceptance activities. Acceptance activities include inspections, tests, or other verification activities.

(b) *Receiving acceptance activities.* Each manufacturer shall establish and maintain procedures for acceptance of incoming product. Incoming product shall be inspected, tested, or otherwise verified as conforming to specified requirements. Acceptance or rejection shall be documented.

(c) *In-process acceptance activities.* Each manufacturer shall establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are documented.

(d) *Final acceptance activities.* Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until:

(1) The activities required in the DMR are completed;

(2) the associated data and documentation is reviewed;

(3) the release is authorized by the signature of a designated individual(s); and

(4) the authorization is dated.

(e) *Acceptance records.* Each manufacturer shall document acceptance activities required by this part. These records shall include:

(1) The acceptance activities performed;

(2) the dates acceptance activities are performed;

(3) the results;

(4) the signature of the individual(s) conducting the acceptance activities; and

(5) where appropriate the equipment used. These records shall be part of the DHR.

820.86 Acceptance status.

Each manufacturer shall identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of product with acceptance criteria. The identification of acceptance status shall be maintained throughout manufacturing, packaging, labelling, installation, and servicing of the product to ensure that only product which has passed the required acceptance activities is distributed, used, or installed.

Subpart I-Nonconforming Product

820.90 Nonconforming product.

(a) *Control of nonconforming product*. Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.

(b) *Nonconformity review and disposition.* (1) Each manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. The procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be documented. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.

(2) Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the DHR.

Subpart J-Corrective and Preventive Action

820.100 Corrective and preventive action.

(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;

(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

(5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;

(6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and

(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

(b) All activities required under this section, and their results, shall be documented.

Subpart K-Labelling and Packaging Control

820.120 Device labelling.

Each manufacturer shall establish and maintain procedures to control labelling activities.

(a) *Label integrity.* Labels shall be printed and applied so as to remain legible and affixed during the customary conditions of processing, storage, handling, distribution, and where appropriate use.

(b) *Labelling inspection.* Labelling shall not be released for storage or use until a designated individual(s) has examined the labelling for accuracy including, where applicable, the correct expiration date, control number, storage instructions, handling instructions, and any additional processing instructions. The release, including the date and signature of the individual(s) performing the examination, shall be documented in the DHR.

(c) *Labelling storage.* Each manufacturer shall store labelling in a manner that provides proper identification and is designed to prevent mix ups.

(d) *Labelling operations.* Each manufacturer shall control labelling and packaging operations to prevent labelling mix ups. The label and labelling used for each production unit, lot, or batch shall be documented in the DHR. (e) Control number. Where a control number is required by 820.65, that control number shall be on or shall accompany the device through distribution.

820.130 Device packaging.

Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

Subpart L-Handling, Storage, Distribution, and Installation

820.140 Handling.

Each manufacturer shall establish and maintain procedures to ensure that mix ups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling.

820.150 Storage.

(a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mix ups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate.

(b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms.

820.160 Distribution.

(a) Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed and that purchase orders are reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Where a device's fitness for use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed.

(b) Each manufacturer shall maintain distribution records which include or refer to the location of:

(1) The name and address of the initial consignee;

(2) The identification and quantity of devices shipped;

(3) The date shipped; and

(4) Any control number(s) used.

820.170 Installation.

(a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the ddevice or otherwise make them available to the person(s) installing the device.

(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.

Subpart M-Records

820.180 General requirements.

All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of FDA designated to perform inspections. Such records, including those not stored at the inspected establishment, shall be made readily available for review and copying by FDA employee(s). Such records shall be legible and shall be stored to minimize deterioration and to prevent loss. Those records stored in automated data processing systems shall be backed up.

(a) *Confidentiality.* Records deemed confidential by the manufacturer may be marked to aid FDA in determining whether information may be disclosed under the public information regulation in part 20 of this chapter.

(b) *Record retention period.* All records required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer.

(c) *Exceptions.* This section does not apply to the reports required by 820.20(c) Management review, 820.22 Quality audits, and supplier audit reports used to meet the requirements of 820.50(a) Evaluation of suppliers, contractors, and consultants, but does apply to procedures established under these provisions. Upon request of a designated employee of FDA, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.

820.181 Device master record.

Each manufacturer shall maintain device master records (DMR's). Each manufacturer shall ensure that each DMR is prepared and approved in accordance with 820.40. The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications; (b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

(d) Packaging and labelling specifications, including methods and processes used; and

(e) Installation, maintenance, and servicing procedures and methods.

820.184 Device history record.

Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include, or refer to the location of, the following information:

(a) The dates of manufacture;

(b) The quantity manufactured;

(c) The quantity released for distribution;

(d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR;

(e) The primary identification label and labelling used for each production unit; and

(f) Any device identification(s) and control number(s) used.

820.186 Quality system record.

Each manufacturer shall maintain a quality system record (QSR). The QSR shall include, or refer to the location of, procedures and the documentation of activities required by this part that are not specific to a particular type of device(s), including, but not limited to, the records required by 820.20. Each manufacturer shall ensure that the QSR is prepared and approved in accordance with 820.40.

820.198 Complaint files.

(a) Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:

(1) All complaints are processed in a uniform and timely manner;

(2) Oral complaints are documented upon receipt; and

(3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 or 804 of this chapter, Medical Device Reporting.

(b) Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.

(c) Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

(d) Any complaint that represents an event which must be reported to FDA under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise clearly identified. In addition to the information required by 820.198(e), records of investigation under this paragraph shall include a determination of:

(1) Whether the device failed to meet specifications;

(2) Whether the device was being used for treatment or diagnosis; and

(3) The relationship, if any, of the device to the reported incident or adverse event.

(e) When an investigation is made under this section, a record of the investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include:

(1) The name of the device;

(2) The date the complaint was received;

(3) Any device identification(s) and control number(s) used;

(4) The name, address, and phone number of the complainant;

(5) The nature and details of the complaint;

(6) The dates and results of the investigation;

(7) Any corrective action taken; and

(8) Any reply to the complainant.

(f) When the manufacturer's formally designated complaint unit is located at a site separate from the manufacturing establishment, the investigated complaint(s) and the record(s) of investigation shall be reasonably accessible to the manufacturing establishment.

(g) If a manufacturer's formally designated complaint unit is located outside of the United States, records required by this section shall be reasonably accessible in the United States at either:

(1) A location in the United States where the manufacturer's records are regularly kept; or

(2) The location of the initial distributor.

[61 FR 52654, Oct. 7, 1996, as amended at 69 FR 11313, Mar. 10, 2004]

Subpart N-Servicing

820.200 Servicing.

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.

(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.

(c) Each manufacturer who receives a service report that represents an event which must be reported to FDA under part 803 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

(d) Service reports shall be documented and shall include:

(1) The name of the device serviced;

(2) Any device identification(s) and control number(s) used;

(3) The date of service;

(4) The individual(s) servicing the device;

(5) The service performed; and

(6) The test and inspection data.

[61 FR 52654, Oct. 7, 1996, as amended at 69 FR 11313, Mar. 10, 2004]

Subpart O-Statistical Techniques

820.250 Statistical techniques.

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

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Title 21: Food and Drugs

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

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Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.
Source: 43 FR 45077, Sept. 29, 1978, unless otherwise noted.

Subpart A—General Provisions

211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(c) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

[43 FR 45077, Sept. 29, 1978, as amended at 62 FR 66522, Dec. 19, 1997; 69 FR 29828, May 25, 2004]

211.3 Definitions.

The definitions set forth in 210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

211.22 Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labelling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mix ups between different components, drug product containers, closures, labelling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labelling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix ups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labelling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labelling before disposition;

(3) Storage of released components, drug product containers, closures, and labelling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labelling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

211.44 Lighting.

Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

211.48 Plumbing.

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

[43 FR 45077, Sept. 29, 1978, as amended at 48 FR 11426, Mar. 18, 1983]

211.50 Sewage and refuse.

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities.

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accesible to working areas.

211.56 Sanitation.

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labelling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungiciides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

211.58 Maintenance.

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

211.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In

such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

Subpart E—Control of Components and Drug Product Containers and Closures

211.80 General requirements.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labelling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of 211.80.

211.80. General requirements

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the deposition of each lot. Each lot shall be appropriately identified as its status (i.e. quarantined, approved, or rejected).

211.82 Receipt and storage of untested components, drug product containers, and closures

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labelling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined as appropriate, and released. Storage within the area shall conform to the requirements of 211.80.

211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by 211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

[43 FR 45077, Sept. 29, 1978, as amended at 63 FR 14356, Mar. 25, 1998]

211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

211.87 Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

211.89 Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.94 Drug product containers and closures.

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F—Production and Process Controls

211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

211.101 Charge-in of components.

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labelled or established amount of active ingredient.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code;

(2) Receiving or control number;

(3) Weight or measure in new container;

(4) Batch for which component was dispensed, including its product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

(1) The component was released by the quality control unit;

(2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly identified.

(d) Each component shall be added to the batch by one person and verified by a second person.

211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

211.105 Equipment identification.

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

211.113 Control of microbiological contamination.

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

211.115 Reprocessing.

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.
(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labelling Control

211.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labelling and packaging materials; such written procedures shall be followed. Labelling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labelling of a drug product.

(b) Any labelling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labelling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labelling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labelling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

(e) Obsolete and outdated labels, labelling, and other packaging materials shall be destroyed.

(f) Use of gang-printed labelling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labelling from gang-printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labelling is used, packaging and labelling operations shall include one of the following special control procedures:

(1) Dedication of labelling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labelling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labelling during or after completion of finishing operations for hand-applied labelling. Such examination shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labelling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993]

211.125 Labelling issuance.

(a) Strict control shall be exercised over labelling issued for use in drug product labelling operations.

(b) Labelling materials issued for a batch shall be carefully examined for identity and conformity to the labelling specified in the master or batch production records.

(c) Procedures shall be used to reconcile the quantities of labelling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labelling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with 211.192. Labelling reconciliation is waived for cut or roll labelling if a 100-percent examination for correct labelling is performed in accordance with 211.122(g)(2).

(d) All excess labelling bearing lot or control numbers shall be destroyed.

(e) Returned labelling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labelling; such written procedures shall be followed.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

211.130 Packaging and labelling operations.

There shall be written procedures designed to assure that correct labels, labelling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mix ups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labelling operations to preclude mislabelling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labelling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labelling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labelling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(a) *General.* The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-evident packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labelled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) Requirements for tamper-evident package. (1) Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(2) In addition to the tamper-evident packaging feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.

(c) *Labelling.* (1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

(i) Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;

(ii) Is prominently placed on the package; and

(iii) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(2) If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labelling statement. For example, the labelling statement on a bottle with a shrink band could say “For your protection, this bottle has an imprinted seal around the neck.”

(d) *Request for exemptions from packaging and labelling requirements*. A manufacturer or packer may request an exemption from the packaging and labelling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a “Request for Exemption from the Tamper-Evident Packaging Rule.” The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-evident packaging or labelling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

(e) *OTC drug products subject to approved new drug applications*. Holders of approved new drug applications for OTC drug products are required under 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labelling required by this regulation may be made before FDA approval, as provided under 314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under 314.70(b) of this chapter.

(f) *Poison Prevention Packaging Act of 1970*. This section does not affect any requirements for “special packaging” as defined under 310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 1970.

(Approved by the Office of Management and Budget under OMB control number 0910–0149)
[54 FR 5228, Feb. 2, 1989, as amended at 63 FR 59470, Nov. 4, 1998]

211.134 Drug product inspection.

(a) Packaged and labelled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.

(b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labelling.

(c) Results of these examinations shall be recorded in the batch production or control records.

211.137 Expiration dating.

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labelling, as determined by stability studies described in 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labelling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labelling in accordance with the requirements of 201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labelled “No U.S. Standard of Potency” are exempt from the requirements of this section.

(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labelling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labelling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995]

Subpart H—Holding and Distribution

211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

211.150 Distribution procedures.

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labelling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labelling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of shortlived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant critieria.

211.166 Stability testing.

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labelling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labelled “No U.S. Standard of Potency” are exempt from the requirements of this section.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

211.170 Reserve samples.

(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labelling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product. (2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

[48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan. 20, 1995]

211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in `Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD–470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

[43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990; 66 FR 56035, Nov. 6, 2001; 69 FR 18803, Apr. 9, 2004]

Subpart J—Records and Reports

211.180 General requirements.

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labelling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labelling.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995] 211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labelling records.

These records shall include the following:
(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labelling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

(b) The results of any test or examination performed (including those performed as required by 211.82(a), 211.84(d), or 211.122(a)) and the conclusions derived therefrom.

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

(d) Documentation of the examination and review of labels and labelling for conformity with established specifications in accord with 211.122(c) and 211.130(c).

(e) The disposition of rejected components, drug product containers, closure, and labelling.

211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required;

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labelling signed and dated by the person or persons responsible for approval of such labelling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:
(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labelling area before and after use;

(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(8) Complete labelling control records, including specimens or copies of all labelling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation;

(12) Any investigation made according to 211.192.

(13) Results of examinations made in accordance with 211.134.

211.192 Production record review.

All drug product production and control records, including those for packaging and labelling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.

211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists International, Book of Methods, (1) or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

(1) Copies may be obtained from: Association of Official Analytical Chemists International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877.

(3) A statement of the weight or measure of sample used for each test, where appropriate.

(4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

(7) The initials or signature of the person who performs each test and the date(s) the tests were performed.

(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with 211.166.

[43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990; 65 FR 18889, Apr. 10, 2000; 70 FR 40880, July 15, 2005]

211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers. (Approved by the Office of Management and Budget under control number 0910–0139)

[49 FR 9865, Mar. 16, 1984]

211.198 Complaint files.

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with 310.305 and 514.80 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files

are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.

(2) Where an investigation under 211.192 is conducted, the written record shall include the findings of the investigation and follow up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with 211.180(c).

(3) Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

[43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986; 68 FR 15364, Mar. 31, 2003]

Subpart K—Returned and Salvaged Drug Products

211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labelling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

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