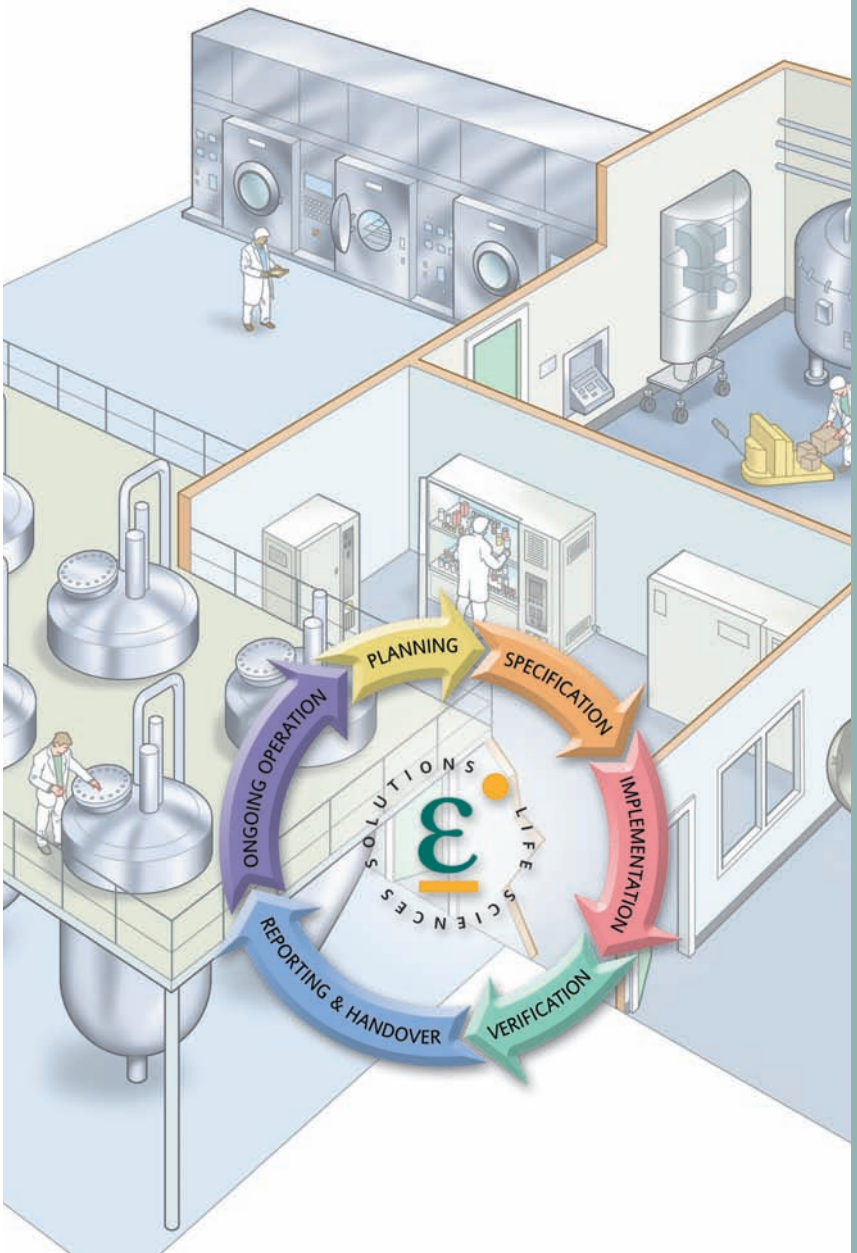
EUROTHERM® FLEXIBLE SOLUTIONS

Pharma Reference Guide



invensys®
EUROTHERM®

GAMP5

Validatable Records

Validatable Audit Trails

Store & Forward Data Integrity

EUROTHERM® FLEXIBLE SOLUTIONS

Life Sciences

- 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 platform
- 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

Documentation

- Life Sciences Catalogue
- Life Sciences Brochure
- Building Management Systems & Environmental Monitoring Systems Brochure
- Eycon Brochure
- 6000 Series Brochure
- 6000 Series Recorders and 21 CFR Part 11
- 3000 Series Brochure
- 2000 Series Brochure

Visit **www.eurotherm.co.uk/products** to download

Introduction

FOR EUROTHERM the definition of Life Sciences covers the following market areas:


Pharmaceutical


Medical Devices


Healthcare


Cosmetics

We have been active within all of these industries for many years and together they constitute a complete global business unit.

The purpose of the 'Pharma Reference Guide' is to provide our customers categorised within all the sectors above with a broad overview of the business and legislative issues that we consider significant and which play a major role in governing the marketing input and subsequent R&D activities within our company.

The 'Pharma Reference Guide' was originally published for use as an internal training document within our business unit but we have also used it for customer training and it is because of the feedback from our customers that we decided to publish the document.

We hope that you will find it a useful digest of the pharmaceutical business and that you will consider Eurotherm for future projects within your company.

Jargon Buster

21 CFR Part 11	FDA's regulation on Electronic Records and Electronic Signatures
ABPI	Association of the British Pharmaceutical Industry
Annex 11	Good Manufacturing Practice for Computerised Systems (Europe)
API	Active Pharmaceutical Ingredient
CFR	Code of Federal Regulations (FDA regulations are all in 21 CFR)
CTD	Common Technical Document (international format for new drug submissions)
EMEA	European Medicines Evaluation Agency (EEC Regulator)
FDA	Food and Drug Administration (US Regulator)
GAMP	Good Automated Manufacturing Practice as described in GAMP5: A Risk-Based Approach to Compliant GxP Computerised Systems
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GHTF	Global Harmonisation Task Force
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GxP/cGxP	Current Good Practice
HC-SC	Health Canada – Santé Canada (canadian Regulator)
HVAC	Heating, Ventilation and Air Conditioning Systems
ICH	International Conference on Harmonisation
IQ	Installation Qualification
MCC	Medicine Dictionary for Regulatory Activities (MedDRA)
MedDRA	Medicines and Healthcare Products Regulatory Agency (UK Regulator – formerly the MCA and the MDA)
MHLW	Ministry of Health, Labour and Welfare (Japanese Regulator)
MKT	Mean Kinetic Temperature
NIHS	National Institute of Health Science (Japanese Regulator)
OQ	Operational Qualification
PAT	Process Analytical Technology
PhRMA	Pharmaceutical Research and Manufacturers of America
PIC/S	Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme PQ
PQ	Performance Qualification
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration (Australian Regulator)
URS	User Requirements Specification
VMP	Validation Master Plan
WFI	Water For Injection

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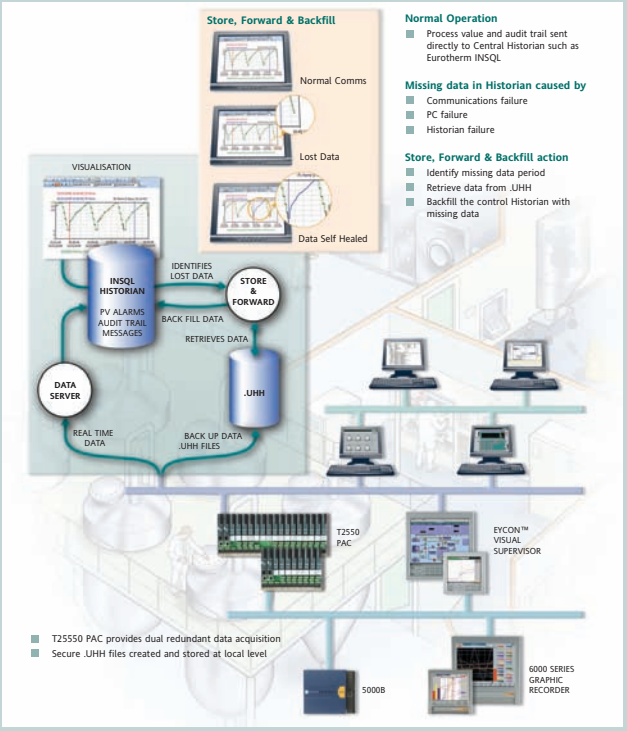
Self Healing Data Archiving with "Store & Forward"

'Store & Forward' is a self healing 21 CFR Part 11 data archiving system that automatically stores data during a communications failure and then forwards this to the configured server when communications have been reinstated.

This results in secure electronic recording with total data integrity.



Page from the Eurotherm Store & Forward Brochure

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 (F°) calculation
- Remote viewing via Bridge software
- Time Synchronisation
- Offline data viewing via Review software
- Report generation
- Direct printer output
- Support for Email/SMS notification

6180A Graphic Recorder

5000B Data Acquisition Unit

1 Healthcare Industries Overview

The Healthcare industry is often conveniently split into healthcare providers (hospitals, general practitioners, dentists etc.) and healthcare suppliers (who manufacture the products used by the providers).

The suppliers are also frequently divided by type of product as these are often regulated by different agencies (eg medicines / medical devices / blood products in the UK, drugs / biologics / medical devices in the US).

MEDICINES - a substance which ends up inside your body in an attempt to make you better

"Any substance or combination of substances presented for treating or preventing disease ... or which may be administered ... with a view to making a diagnosis or to restoring, correcting or modifying physiological functions ..." (MHRA)

DRUGS - medicines with a chemical origin

BIOLOGICS – medicines with a human or animal origin

"a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." (US Health Service Act)

MEDICAL DEVICES – any product which isn't a medicine but is used to treat you in some way

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease." (US Federal Food Drug & Cosmetic Act)

US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

EurothermSuite

EurothermSuite is the software solution to match your evolving requirements and is equally applicable to simple I/O, indicators and loop controllers as well as data management, panel displays, redundant controllers and complete networked.

Single loop to plant-wide, software solution

- Visualise your automation system
- Simple structured approach
- Scalable solution
- Quick to learn
- Configuration tools
- Control and application modules
- Minimal engineering effort
- Single point of configuration
- Common database

Control Record Visualise Automate

- Open access
- OPC standards inbuilt
- On-Line configuration
- Easy and intuitive functionality
- Auto configuration

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
- XGA touchscreen display to IP65
- Secure data logging and trending
- Recipe and alarm management

Eycon™ Visual Supervisor

21 CFR Part 11
ENHANCED FOR

21 CFR Part 11 – 'Ready to use'

The Auditor feature on the visual supervisor has been specifically designed to meet the requirement of the FDAs 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

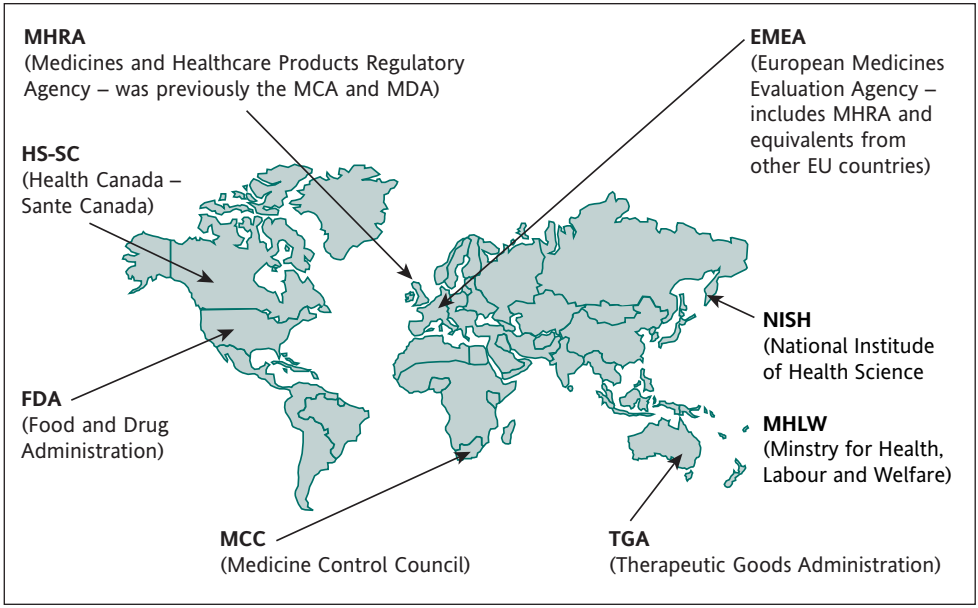
Scalable Architecture

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.

2 Regulators

Almost every country has standards of safety, quality, performance and effectiveness for medicines, healthcare products and medical equipment, and also regulations to ensure that they are used safely.

Regulatory bodies exist to ensure that these standards are enforced for both locally manufactured products and imported products. In order to sell a healthcare product into a country, a supplier must demonstrate compliance with the appropriate standards (so, for example, to sell into the lucrative US market, a drug company must first get its product approved by the FDA).



US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

THERE ARE a number of initiatives to harmonise the requirements of different regulators and to allow one regulator to recognise an approval granted by another.

The following are particularly noteworthy:

International Conference on Harmonisation (ICH)

ICH works to bring together government regulators and drug industry representatives from the U.S., the European Union, and Japan to make the international drug regulatory process more efficient and uniform. Some ICH projects include:

Medical Dictionary for Regulatory Activities (MedDRA) - a new international medical terminology designed to improve the electronic transmission of regulatory information and data worldwide. It will be used to collect, present, and analyse information on medical products during clinical and scientific reviews and marketing. It will be particularly critical in the electronic transmission of adverse event reporting and coding of clinical trial data.

Common Technical Document (CTD) - an international standard format for submitting safety and efficacy information about a new drug.

Global Harmonisation Task Force (GHTF)

GTHF was conceived in 1992 in an effort to respond to the growing need for international Harmonisation in the regulation of medical devices. It brings together regulatory officials and industry representatives from the European Union, the United States of America, Canada, Japan and Australia.

International Conference on Harmonisation (ICH) **www.ghtf.org**
International Conference on Harmonisation **www.ich.org**

3 Life-Cycle of a Drug “Test Tube to Tablet”

It can take up to 12 years to develop a new drug. Each year, the R&D teams of a large pharmaceutical company will generate around 10,000 new potential drug molecules. Of these, only one or two will get as far as being given a license. Only one in seven of these licensed medicines goes on to be a commercial success.

Initial Research

The research team look for compounds which might treat a given disease. Potential drug molecules are identified and screened for likely effects by computer modelling. Promising drugs are then tested using chemical and/or biological assay techniques to see whether they do act on the desired target. Potential drugs which still look promising are patented to prevent their use by other companies.

Pre-Clinical Development

Small quantities of the potential drug are tested on cell cultures for both therapeutic effects and toxicity. Molecules which appear to have the desired properties are then tested on animals. Data from the pre-clinical trials is used to apply for a certificate to conduct clinical trials.

US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

	Apply for Clinical Trail Certificate	Certificate Granted	Apply for Product License	License Granted	Apply for Patent
Research Activities	Initial Research (identifies possible target molecules)	Pre-clinical Development (testing on cell cultures and animals)	Phase I Clinical Trails (tested in healthy volunteers)	Phase II Clinical Trails (tested in a small group of patients)	Phase III Clinical Trails (tested in healthy volunteers)	Phase IV Clinical Trails (tested in healthy volunteers)
Manufacturing Activities	(Research Laboratory)		Small Scale Laboratory		Large Scale Laboratory/ Pilot Plant	Full Scale Manufacture
Approx No. of Molecules	10,000	10	5	2	1	1
Approx Cost of Development		£50M			£195M	£350M
Approx Timescale (yrs)	1 2 3 4		5 6	7 8	9 10	11 12

Data on molecule numbers, costs, timescales taken from the Association of the British Pharmaceutical Industry (ABPI) website

Clinical Trials – Phase I

The potential drug is administered to a small number of healthy, informed volunteers under medical supervision. If the substance behaves in the predicted way, it then moves on to phase II trials.

Clinical Trials – Phase II

The potential drug is used to treat a small group (typically up to 200) of informed patients. If the drug appears to work when compared to a control group and does not produce unacceptable side effects, it then moves on to phase III trials.

Clinical Trials – Phase III

The trial is broadened to treat a much larger group (typically 1000+) of patients. If a statistical analysis shows that the drug is effective and safe then the data is used to apply for a commercial license for the product.

Clinical Trials – Phase IV

Once the drug is on the market, monitoring for any adverse effects continues.

The Association of the British Pharmaceutical Industry (ABPI) **www.abpi.org.uk**
Pharmaceutical Research and Manufacturers of America (PhRMA) **www.phrma.org**

4 Manufacturing

4.1 Active Pharmaceutical Ingredients

An Active Pharmaceutical Ingredient (API) is defined as "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.

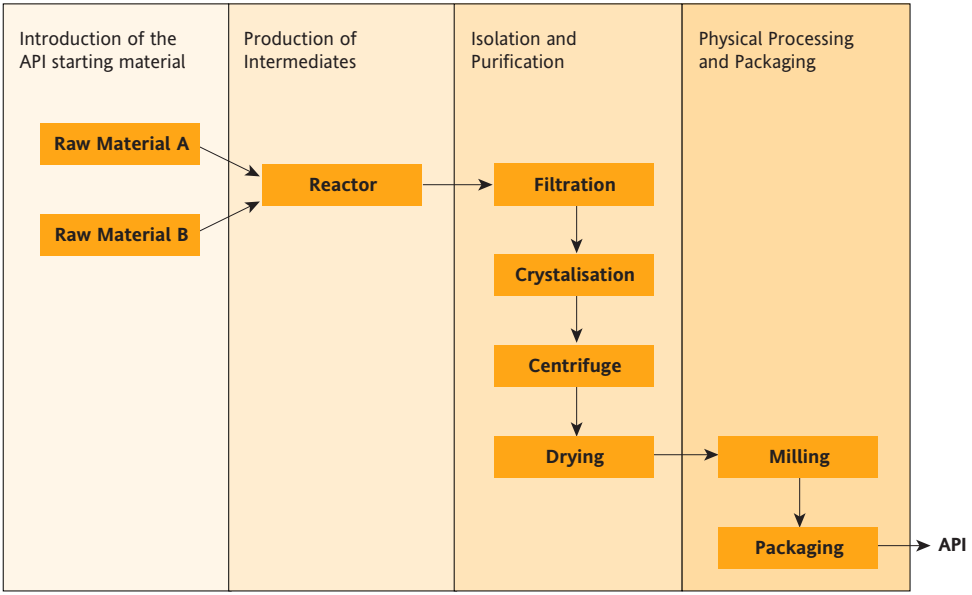
APIs can be manufactured by chemical synthesis, extraction, cell culture / fermentation, recovery from natural sources, or any combination of these. API manufacture is also referred to as 'primary manufacture'.

The following is reproduced from the PIC/S Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients and summarises the steps involved in different types of API manufacture.

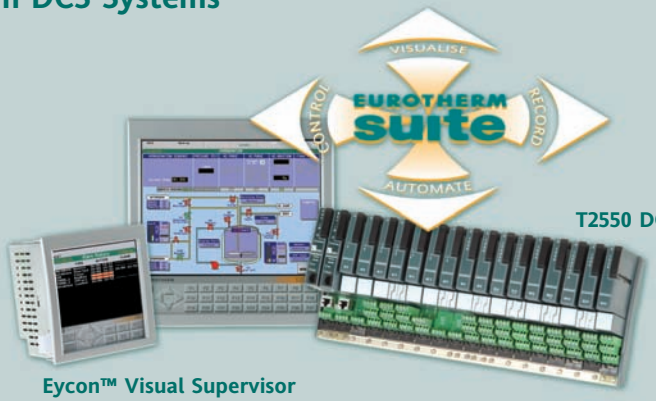
Type of Manufacturing	**Application of this Guide to steps (shaded) used in this type of manufacturing** *Shaded background means that the step is subject to the controls detailed in the Guide				
Chemical manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of intermediate	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 plants	Cutting and initial extraction	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	Collection of plants and/or cultivation and harvesting	Cutting comminuting			Physical processing and packaging
Biotechnology fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and or fermentation	Isolation and purification packaging	Physical processing and
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of working cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

Increasing GMP requirements

Example API Manufacturing Process



Eurotherm DCS Systems



PIC/S Guide to API manufacture **www.picscheme.org/docs/pdf/gmpapi.pdf**

4.2 Secondary Manufacture

The active ingredient is the output of the primary manufacturing stage. However, it still needs to be turned into a suitable form to give to a patient. This is done in secondary manufacture where the active ingredient is mixed with excipients (non active ingredients which bind the active ingredients and give them suitable physical properties) and turned into individual doses. Active pharmaceutical ingredients and excipients may be collectively referred to as 'bulk pharmaceutical chemicals'.

All steps during secondary manufacturing are subject to codes of Good Manufacturing Practice (GMP) defined by industry regulators.

Doses of a drug can be given in many different forms and the secondary manufacturing stages clearly depend on the selected drug delivery method – both its physical form and whether it is required to be sterile.

Some example delivery methods are given below:

Tablets

Creams & Ointments

Injections
(must be sterile)

Capsules

Patches

Infusions
(must be sterile)

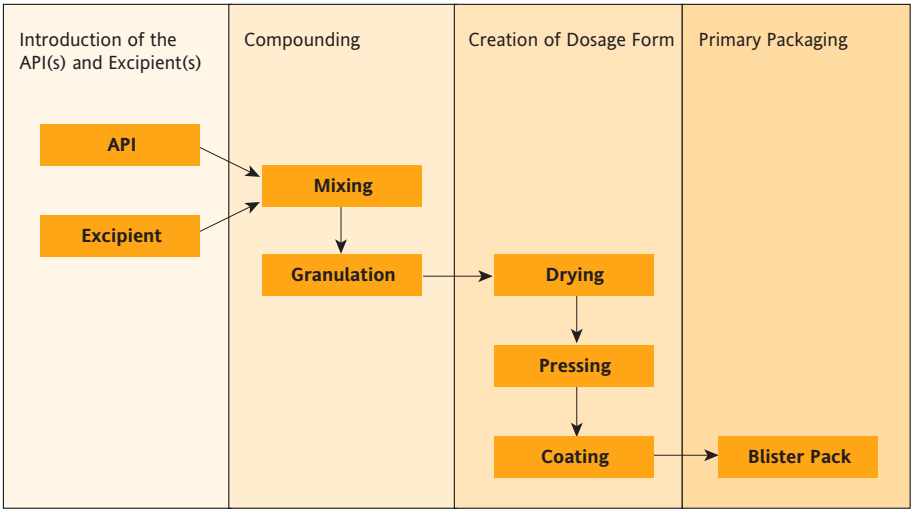
Solutions & Suspensions

Eye drops & Ointments
(must be sterile)

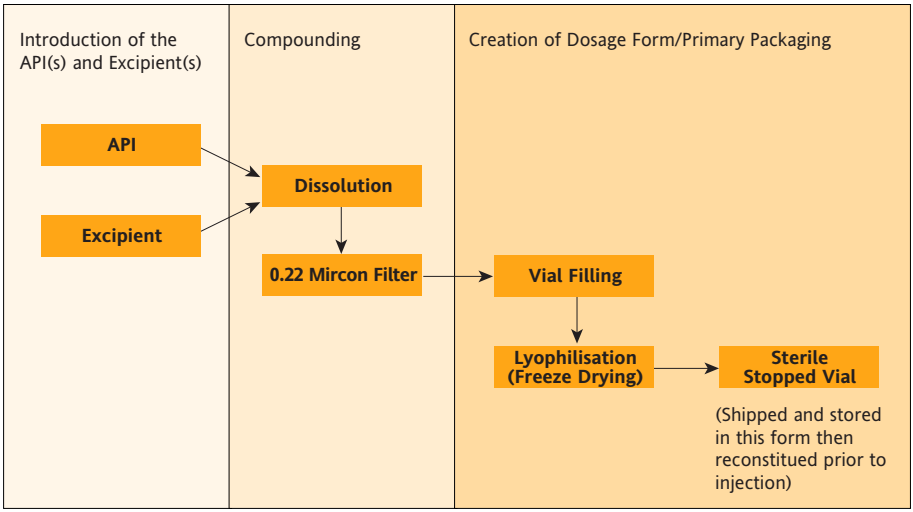
Oral Dosage Forms
(Designed for absorption through the alimentary canal)

US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

Example Secondary Manufacturing Process – Tablets



Example Secondary Manufacturing Process – Sterile parenteral for injection



The Association of the British Pharmaceutical Industry (ABPI) **www.abpi.org.uk**
Pharmaceutical Research and Manufacturers of America (PhRMA) **www.phrma.org**

4.3 Packaging

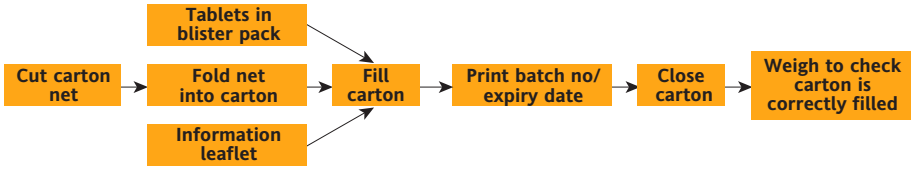
In order to become a finished pharmaceutical product, the dosage forms created during secondary manufacture need to be packaged.

PRIMARY PACKAGING is the packaging used to form a container for the product and which is in direct contact with the product (eg. sterile vial, medicine bottle, tablet blister pack).

Example Primary Packaging – Tablets

SECONDARY PACKAGING is any subsequent packaging which helps to inform about, display and protect the product. It includes all required labelling and information leaflets.

Example Secondary Packaging – Tablets



TERTIARY PACKAGING is any final packaging grouping the products for storage and transportation.

Example Tertiary Packaging – Tablets

US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**
The Association of the British Pharmaceutical Industry (ABPI) **www.abpi.org.uk**
Pharmaceutical Research and Manufacturers of America (PhRMA) **www.phrma.org**

4.4 Biotechnology

The Biotechnology industry uses living organisms, or substances from those organisms, to make or modify products by microbial and biochemical processes. Within biopharmaceuticals, biotechnology is typically used to create an active ingredient for use in drugs or diagnostic testing.

Although there has recently been a rapid expansion in the biotechnology industry (fuelled by new genetic engineering techniques), biotechnology has been around for many years – the extraction of penicillin from the mould Penicillium notatum first took place in the 1930s. Outside of biopharmaceuticals, there is evidence of humans using fermentation to manufacture alcohol over 8000 years ago.

Areas covered by the term biotechnology include, amongst others:

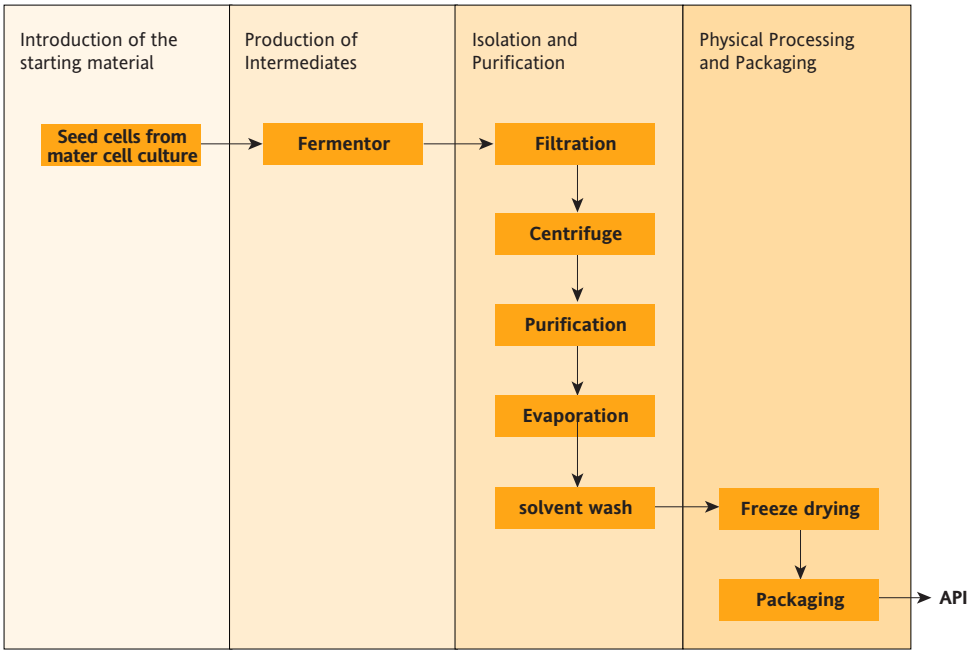
FERMENTATION is the synthesis of organic compounds by micro-organisms. Micro-organisms are grown within an enclosed tank (fermenter) under controlled conditions of aeration, agitation, temperature, and pH. The required active ingredient can then be extracted by filtration and centrifuging ready for purification.

RECOMBINANT DNA TECHNIQUES allow scientists to introduce new genes for useful proteins into the DNA of cells. The cells may be bacteria, fungi or cultures of animal cells. The modified cells can be grown on a large scale (for example by fermentation) to produce proteins in industrial quantities.

CELL FUSION TECHNIQUES involve the fusing together of two or more cells to become a single cell. This technique is particularly important in the production of monoclonal antibodies. Typically, a spleen cell (producing an antibody specific for the antigen of interest) might be fused with with a mouse myeloma cell to produce a hybridoma which has an indefinitely long life because of the myeloma component and which secretes the desired antibody. The fused cells can be grown on a large scale (for example by fermentation) to produce proteins in industrial quantities.

Glossary of biotechnology terms **http://biotechterms.org**
US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

Example Biotechnology Manufacturing Process



The Association of the British Pharmaceutical Industry (ABPI) **www.abpi.org.uk**
Pharmaceutical Research and Manufacturers of America (PhRMA) **www.phrma.org**

4.5 Services

HVAC (Heating, Ventilation and Air Conditioning Systems)

Some aspects of pharmaceutical manufacture require tight control and monitoring of building air supplies. Temperature and humidity control / recording may be required in order to prove that the product has not been exposed to conditions which might cause degradation. Pressure control is used to control air flows so as to contain harmful substances or to maintain sterility.

Some typical areas of concern are given below:

Type of facility	Temperature Control	Humidity Control	Pressure Control
Office	Wide tolerance	Wide tolerance	None
Distribution & Warehousing	Dependant on temperature stability of product	Dependent on effect of humidity on product	None
Animal Housing	Narrow tolerance for animal welfare reason	Wide tolerance	Narrow tolerance to ensure correct air flow and give flexibility to keep different species in the correct environments
Manufacturing	Dependent on process and temperature stability of product	Dependent on process and effect of humidity on product (eg caking of powders)	Dependent on exhaust requirements, containment needs, dust collection
Sterile Manufacturing	Dependent on process and temperature stability of product and ease of microbial growth	Dependent on process and effect of humidity on product – often requires tight tolerance as many sterile products are supplied as freeze-dried powders	Very narrow tolerance in order to ensure correct flows of clean, filtered air and prevent cross contamination.
Biohazard Containment	Dependent on process and temperature stability of product	Dependent on process and effect of humidity on product	Very narrow tolerance to ensure containment

Water

Standards for different water types are laid down in the US and European Pharmacopoeias.

NON-POTABLE WATER should not come into contact with pharmaceutical products.

POTABLE (DRINKING) WATER can come direct from a municipal water system and be used in active pharmaceutical ingredient (API) manufacture but not in the preparation of dosage forms.

PURIFIED WATER has defined limits for bacterial contamination and must be used for preparing final dosage forms. Water can be purified by many techniques including combinations of UV treatment, ozone treatment, ion exchange, reverse osmosis, electrodeionisation, electrodialysis, ultrafiltration and microfiltration.

WATER FOR INJECTION (WFI) has tighter limits on bacterial contamination and additional limits on pyrogens (substances which provoke a fever response in patients – typically a substance which is released during bacterial decay). WFI is purified by distillation or reverse osmosis and must be used for sterile processing (eg for eye drops, and substances intended for injection or intravenous infusion).

Steam

CLEAN STEAM has requirements for chemical purity and is generated from treated water free of volatile additives in special generators designed to ensure it is delivered free of entrained water droplets or air. Clean steam is needed wherever steam enters processing equipment and there is a need to avoid contamination of the product; for example in autoclaves, in clean room humidifiers, or for sterilisation-in-place of equipment or pipe-work.

PURE STEAM has additional requirements (over and above clean steam) that it should not introduce micro-organisms or pyrogens into the product. The condensate from pure steam meets the limits defined for WFI. Pure steam is used in sterile manufacturing operations.

US Food and Drug Administration Website **www.fda.gov**
UK Medicines and Healthcare Products Regulatory Agency **www.mhra.gov.uk**

4.6 Stability Testing

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 recommend storage conditions.

A package of stability data is required before a drug substance or drug product registration application can be made. Stability testing of medicinal products is an area which has been addressed by the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and the ICH final guidance was adopted across Europe, Japan and the United States during 2003; meaning that the same data can now be used to support applications to the FDA (US), the EMEA (Europe) and the MHLW (Japan).

The stability package is normally based on 12 months 'long term study' of batches stored in the intended conditions (eg 5°C for a product intended for storage in a refrigerator) plus a shorter 'accelerated study' at more extreme conditions (eg 25°C/60%RH a product intended for storage in a refrigerator). The data from the accelerated study can be used to asses the impact on shelf life of short term excursions from the intended conditions – for example as often happens during shipping.

If a shelf life of over 12 months is being proposed, then the long term study also needs to continue after product registration to prove stability over the full shelf life.

Data Availability and Security

Since even accelerated trials involve 6 months of data, high availability over long periods is a requirement. Many customers require UPS support of data gathering and local data storage to protect against data loss during network outage.

Since the data has to be stored electronically in order to be useful for performing calculations, the electronic version of the data is used to perform regulated activities and 21 CFR part 11 is a requirement.

Alarms and Excursions

Most companies require alarms on excursion conditions being breached (usually a set temperature or humidity for a particular time). Some companies want more complex logic (eg 'delay the alarm if the room door is known to be open') or alarms based on rolling yearly MKT. A comprehensive user requirements specification can be vital in deciding which product is the best fit for the customer's needs.

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) **www.ich.org**

Mean Kinetic Temperature (MKT)

When assessing the stability of a product, it is important to know the relative effect of storage at different temperatures. Degradation typically happens twice as fast for every 10°C increase in temperature so high temperatures clearly have a much greater effect than would be allowed for if we just took the ordinary 'average' of the temperature through the storage period. Mean kinetic temperature is a way of calculating the 'average' temperature in order to take into account the actual thermal challenge resulting from a range of temperatures during the storage period.

It should be noted that although the MKT formula is well defined, the interpretation of how to apply it in real situations is not. Different pharmaceutical companies use different periods for the temperatures which are fed into the formula; different combinations of max/min/average for the periods; different sample rates for calculating max/min/average; and different methods of combining information from several sensors in a single room.

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

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

Mean Kinetic Temperature (MKT) Calculation

MKT expresses the cumulative thermal stress experienced by a product at varying temperatures during storage and distribution.

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

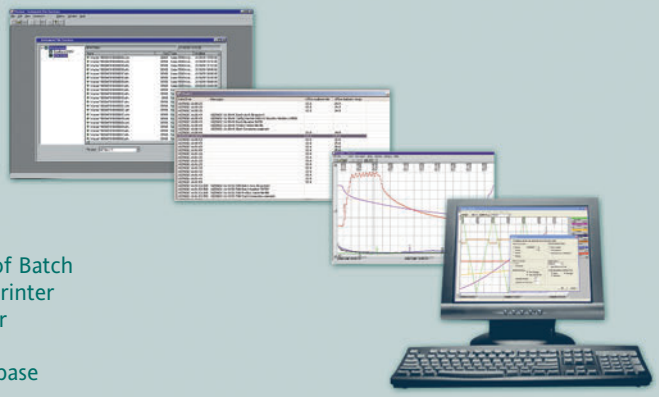
- All sample values fed into formula
- Maximum/minimum samples fed into formula separately (recommended by the FDA)
- Arithmetic mean of maximum and minimum fed into formula (recommended in the US Pharmacopeia and by the UK MCA)

Eurotherm 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

Review

Eurotherm Review is a PC based Software package that allows the display and printing of archived data files from Eurotherm's 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.



Review Full features:

- Automatic Print at end of Batch
- Auto Print to specified Printer
- Auto Print to PDF printer
- Spreadsheet View
- Auto Archive from Database

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

5 The FDA

5.1 'Predicate Rules'

What is a 'Predicate Rule'?

In order to understand FDA rule-making and guidance on using computerised systems within the regulated environment (eg. 21 CFR part 11 on use of electronic records and electronic signatures) it is necessary to understand that these rules are an extension of the 'predicate rules' which describe requirements regardless of whether the activities are manual or automated.

Predicate rules include those contained in the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act and FDA regulations contained in the Code of Federal Regulations - Title 21 - Food and Drugs.

Which Predicate Rules Impact on Automated Systems?

For drug manufacturing, the predicate rules are contained in:

- 21 CFR part 210 Current good manufacturing practice in manufacturing, processing packing, or holding of drugs; general
- 21 CFR part 211 Current good manufacturing practice for finished pharmaceuticals

Note that for other product categories the predicate rules will be different (for example 21 CFR part 820 for medical devices). The predicate rules for other areas of activity (eg Good Clinical Practice) are also different. All are available via the FDA website.

Some examples of requirements from 21 CFR parts 210 / 211 with implications for automated manufacturing are listed below:

Specific requirements for automated systems:

211.68 Automatic, mechanical, and electronic equipment (includes requirements for calibration/ inspection, control over who can access master production and control records, input and output checks, maintenance of backups)

Requirements for keeping records ... cleaning activities

211.67 ... Records shall be kept of maintenance, cleaning, sanitising, and inspection ... master records (can include 'recipes' on process control systems)

211.186 ... 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 ... (goes on to detail what needs to be included in the record) ... batch records (can include batch reports, trends, alarm history, etc on process control systems)

211.188 ... 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 ... (goes on to detail what needs to be included in the record)

US Food and Drug Administration Website **www.fda.gov**

5.2 21 CFR Part 11 and Electronic Records

The intention of 21 CFR part 11 is to make "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"

In order to fall within the scope of 21 CFR part 11, a record must:

1) be required as a record under some other FDA (predicate) rule.

2) be kept in electronic format (note that if paper and electronic version are both kept then the electronic record is 'in scope' if it is relied on to perform regulated activities).

The requirements for electronic records can be summarised as follows:

*Note that items marked * are currently subject to 'enforcement discretion' whilst 21 CFR part 11 is re-visited by the FDA. Refer to the guidance on 21 CFR part 11 scope and application. Legacy systems (operational before 21 CFR part 11 came into effect) are also currently subject to 'enforcement discretion'.*

Note also that some of the requirements are procedural rather than technological so a product on its own can only ever 'support compliance' not 'be compliant'.

VALIDATION* *If the system which produced the records has never been validated, who is likely to trust them?*

The validation needs to include checks that the system is able to discern records which have been altered – otherwise the manufacturer is open to the charge of having falsified the record.

INSPECTABILITY* *If the FDA inspector can't read the record then he is not going to trust it!*

The requirements are:

'accurate and complete copies of records in both human readable and electronic form'

'accurate and ready retrieval throughout the records retention period'

CONTROL OF ACCESS *If you can't prove that only authorised people can use the system then how do you prove that the equipment was used by trained personnel using the correct procedures?*

The requirements are:

'Limiting system access to authorised individuals'

'authority checks to ensure that only authorised individuals can use the system...'

'Determination that persons ... have the education, training, and experience to perform their assigned tasks'

'written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures'

'Use of appropriate controls over systems documentation...'

AUDIT TRAIL* *If the actions were supposed to be carried out in a particular time sequence, is there evidence that this actually happened? Is there evidence that the record has not been tampered with?*

The requirements are:

'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.'

AUTOMATIC CHECKS *Did the system have checks built in to prevent wrongful or fraudulent actions?*

The requirements are:

'operational system checks to enforce permitted sequencing of steps and events'

'device checks to determine ... the validity of the source of data input or operational instruction'

ADDITIONAL REQUIREMENTS FOR OPEN SYSTEMS *If the records have been out into an uncontrolled environment, how do we know they didn't get tampered with? It may be appropriate to include controls such as encryption or digital signatures.*

The requirements are:

'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'

21 CFR part 11 is at **www.fda.gov/ora/compliance_ref/part11/**
Guidance on Scope and Application is at: **www.fda.gov/cder/gmp/index.htm**

5.3 21 CFR Part 11 & Electronic Signatures

The intention of 21 CFR part 11 is to make "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"

The requirements where signatures are executed and stored electronically can be summarised as follows:

Note that some of the requirements are procedural rather than technological so a product on its own can only ever 'support compliance' not 'be compliant'.

ACCEPTANCE AS A LEGALLY BINDING SIGNATURE *As with a handwritten signature, the electronic signing has to be accepted by its owner as being legally binding.*

The requirements are:

Users must 'certify ... that the electronic signatures ... are intended to be the legally binding equivalent of traditional handwritten signatures'

TRACEABILITY TO AN INDIVIDUAL *The whole purpose of a signature is to identify the person taking responsibility for an action.*

The requirements are:

Before setting up electronic signature 'organisation shall verify the identity of the individual'

Signatures need to be:

- ***'unique to one individual and shall not be reused by, or reassigned to, anyone else'***
- ***'used only by their genuine owners'***
- ***'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'***

CLARITY OF MEANING *Just as you wouldn't sign a blank cheque, the meaning of a signature needs to be clear when it is executed. Also, just as the bank will not honour an unsigned or undated cheque or one where the amount is not clearly readable, the details of the electronic signature need to be clear within the record which is kept.*

The requirements are:

Record shall contain the following elements:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning associated with the signature'

Signature elements shall be subject to the same controls as for electronic records

LINKING OF SIGNATURE TO RECORD *Just as handwritten signatures are expected to be in ink rather than pencil, electronic signatures need to be indelibly linked to the record to which they refer.*

The requirements are:

'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 ELEMENTS *In order to be considered trustworthy, an electronic signature either needs:*

- a biometric component designed to ensure use by only its genuine owner, or

- At least two separate components (eg ID and password) one of which is known only to the genuine owner.

The requirements are:

'signatures based upon biometrics: 'shall be designed to ensure that they cannot be used by anyone other than their genuine owners'

'signatures not based upon biometrics: 'at least two distinct identification components

SIGNATURE CONTROLS *It is necessary to demonstrate control of the ID / password / token system in order to have confidence that signatures cannot be fraudulently used.*

The requirements are:

'Ensuring that identification code and password issuances are periodically checked, recalled, or revised (eg to cover such events as password aging)'

'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'

'Use of transaction safeguards to prevent unauthorised use ... and report in an immediate and urgent manner any attempts at their unauthorised use.'

'Initial and periodic testing of devices that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorised manner"

21 CFR part 11 is at **www.fda.gov/ora/compliance_ref/part11/**
Guidance on Scope and Application is at: **www.fda.gov/cder/gmp/index.htm**

5.4 The 'PAT' Initiative

A draft guidance document 'PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance' was issued by the FDA in August 2003. The guidance aims to "encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance" and to "alleviate the fear among manufacturers that introducing new manufacturing technologies will result in regulatory impasse".

Process Analytical Technology (PAT) *is a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.*

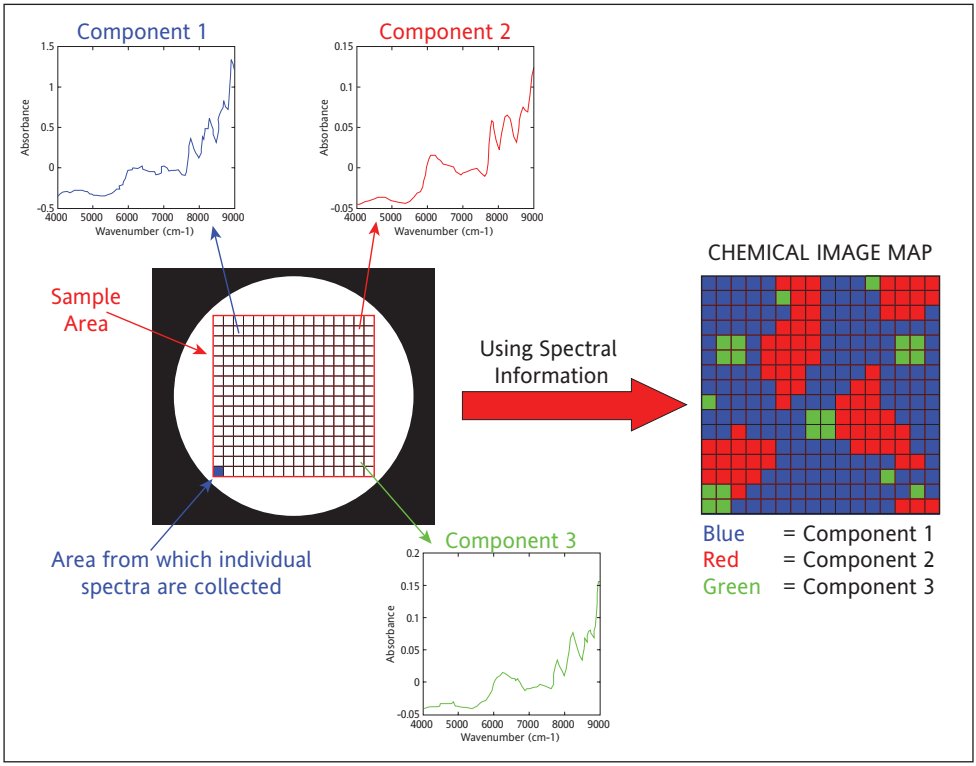
The implementation of PAT can be grouped into four areas:

	Objective	Tools
Understanding the Process	"Can we identify and explain sources of variability in product quality". "Can we predict product quality from the attributes we are able to measure?"	Multivariate Data Acquisition and Analysis during drug development. Experiments based on statistical principles to study the effect and interaction of product and process variables.
Measuring the Process	"Can we measure product quality related attributes on-line during the manufacturing process?"	Process Analysers or Process Analytical Chemistry Tools
Controlling the Process	"Can we implement control strategies based on those measurements?"	Automatic control of critical attributes. Control strategies based on process measurement rather than on timed endpoints
Continuous Improvement and Knowledge Management	"Can we learn from the data the product?" "Can we leverage this knowledge to justify post-approval changes to the manufacturing method?"	Knowledge bases

Example of Process Analytical Technology:

Blending analysis using near infra-red microscopy to plot the relative concentrations of ingredients across a sample and hence decide the end point for the blending operation.

Diagram taken from a presentation by Pfizer to the FDA's PAT team – the whole presentation is available at: **www.fda.gov/ohrms/dockets/ac/01/slides/3799s1_04_Winskill.ppt .**

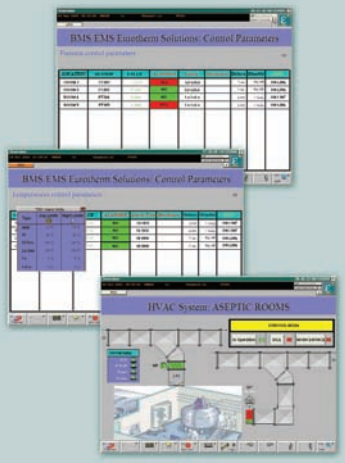


Draft guidance and other information is at **www.fda.gov/cder/OPS/PAT.htm**

BMS/EMS

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

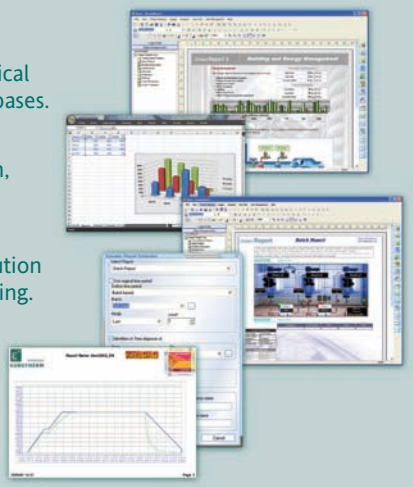
- Scalable from a single room to a plant wide solution
- Simplifies validation using flexible and modular standard functions
- Accurate and effective control of HVAC systems and other related equipment
- Centralised and/or remote control of facilities and equipment
- Real time Monitoring of BMS performance
- 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



Dream Report

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 anybody, anywhere. Built on modern technologies, Dream Report software fits perfectly for both continuous and batch process applications.

- Data Collection
  Dream Report software incorporates a Eurotherm Review driver and report template enabling historical data to be obtained from Eurotherm Review databases.
- Data Logging
  Dream Report software, with its powerful historian, logs by groups, data and alarms
- Report Generation
  In automatic mode, report generation and distribution can be triggered by event or by advanced scheduling.
- Dream Report Objects
  Text Representation
  Tables
  Bars and Pies
  Charts



6 The EMEA and 'Annex11'

The EMEA (European Agency for the Evaluation of Medicinal Products) is a de-centralised body of the European Union. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The agency's Management Board has two representatives from each Member State (eg from the UK's MHRA), from the European Parliament and from the European Commission.

Directives laying down principles of Good Manufacturing Practice were adopted by the European Commission in 1991. Detailed guidelines are published as the Guide to Good Manufacturing Practice, of which Annex 11 is the section covering Computerised Systems. Within the UK, the guidance is published by the MHRA (and formerly by the MCA) in the 'Orange Book'.

The scope of Annex 11 is similar in many ways to that of 21 CFR part 11 though the wording is less prescriptive. The annex covers the following sections:

Principle

Reiterates that the introduction of computerised systems into systems does not alter the need to observe the relevant principles given elsewhere in the Guide.

Personnel

Highlights the need for co-operation between key personnel and those involved with computer systems. Requires appropriate training.

Validation

Requires risk-based validation as part of the computer system lifecycle.

System

Addresses the following:

- Siting of equipment in suitable conditions
- Maintaining an up-to-date, detailed description of the system
- Production of software accordance with a system of Quality Assurance
- Built-in checks of the correct entry and processing of data
- Testing before a system using a computer is brought into use
- System security
- Checking of critical data which are entered manually
- Audit trailing of operator actions
- Procedures for making modifications
- Availability of auditable prints of stored data
- Data security
- Data back-up
- Adequacy of alternative arrangements for systems which need to be operated in the event of a breakdown
- Procedures to be followed if the system fails or breaks down
- Procedures to record and analyse errors and to enable corrective action to be taken
- Clear statements of responsibility if outside agencies are used to provide a computer service
- Restriction to Qualified Persons of the ability to release product for sale

An on-line copy of Annex 11 is available at
http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/anx11en.pdf

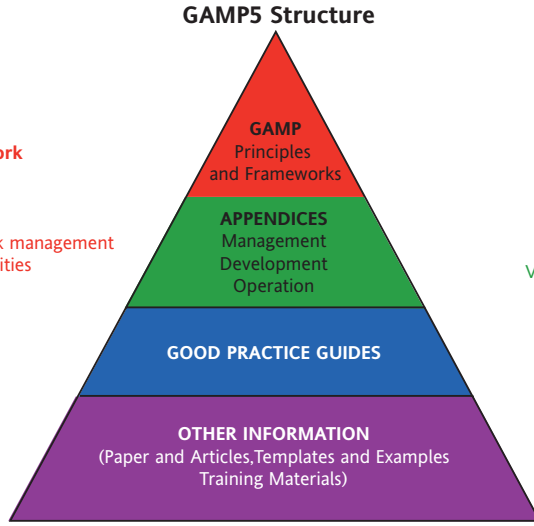
7 GAMP5

7.1 Overview

The 'GAMP' (Good Automated Manufacturing Practice) guides have become the 'de-facto standard' for how to plan and implement computer systems validation within the pharmaceutical industry.

1994–UK Pharmaceutical Industry Computer System Validation Forms set up to create guidelines for the Good Automated Manufacturing Practice (GAMP)

1994 – First draft issue
1995 – Version 1
1996 – Version 2
1998 – Version 3
2001 – Version 4
2008 – Version 5



Principles and Framework
Key concepts
Lifecycle approach
Lifecycle phases
Science based quality risk management
Regulated company activities
Supplier activities
Efficiency improvements

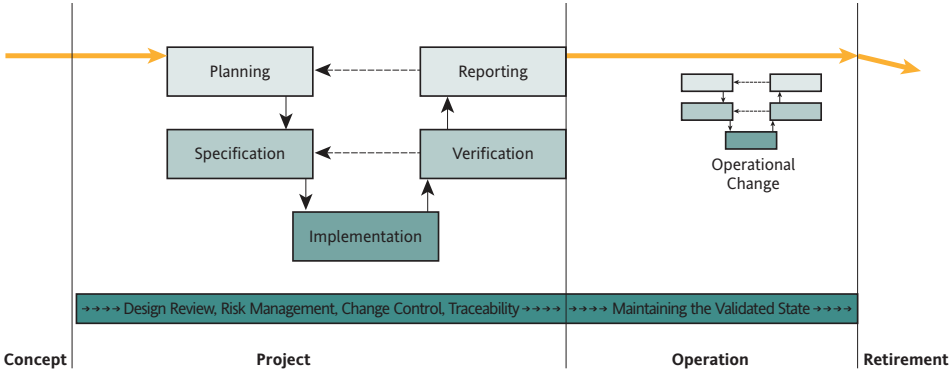
APPENDICES
Management activities
Validation planning/reporting
Risk assessment
Project change control, etc.
Development activities
Specification
Code production
Verification
Operating activities
Service level agreements
Performance monitoring
Archive, etc.

GOOD PRACTICE GUIDES
Electronic data archiving
Testing GxP systems
Global information systems
IT infrastructure control and compliance
Validation of laboratory computerised systems
Risk based approach to electronic records and signatures
Legacy systems
Validation of process control systems
Calibration management

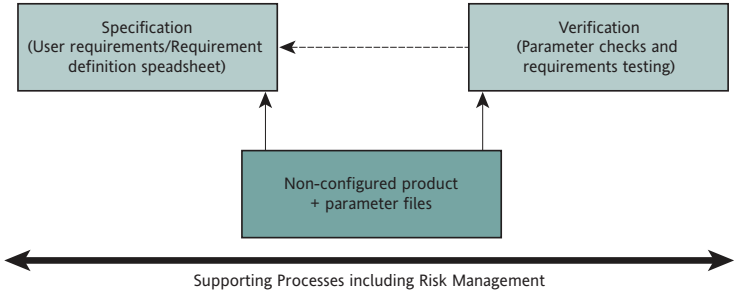
The GAMP5 Guide itself and all of the good practice guides are available from the IPSE **www.ipse.org**

7.2 Lifecycle Requirements

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.



For a single graphic recorder with a single configuration treated as parameterised firmware, the 'supplier' part of the lifecycle might be simplified to:



Although most end users are happy to accept Eurotherm's own documentation provided that it meets GAMP5 guidelines, some insist on documentation written to their own standards. Given this plus the potential differences in required lifecycle complexities, it is vitally important to know the end user's validation requirements – preferably in the form of a formal validation Plan – when quoting for pharmaceutical industry projects.

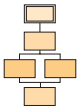
THE GAMP% Guide is available from **www.ispe.org**
Template documents written to meet GAMP5 Guidelines are available via Eurotherm Sharepoint

7.3 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		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

7.4 Testing Requirements

The scope and rigour of testing is dependent on risk to product quality, patient safety and data integrity. This risk is typically assessed be looking at the potential impact (something only the end user can assess), the likelihood of failure (related to the method of implementation) and the probability of detection.

Testing is expected to form part of the formal development lifecycle and to be against pre-approved test scripts written to test documented requirements. It is also expected that tests will be traceable to requirements and vice versa.

In general testing processes from small simple elements towards integration of the whole system. The diagram opposite is an example for a process control system.

Test phasing should be organised to avoid duplication of effort (a) between Eurotherm tests (for example SAT does not need t repeat the whole of FAT, just those elements which may be affected by the transfer to the site environment) and (b) between Eurotherm and end user (for example by splitting site testing into 'installation and 'operation' phases if the customer wants to leverage these as part of his 'IQ' and 'OQ'.

Further details are in GAMP5 Appendix D5 and the Good Practice Guide 'Testing of GxP Systems'.

Test Specification Requirements

- Detail of the test environment to be used including requirements for hardware, test equipment, software, test software, test datasets, base documentation)
- Tracibility of tests to requirements
- Uniquely referenced test scripts which detail any pre-requisites, instructions for performing the test, data to be recorded and the acceptance criteria

Test Execution Requirements

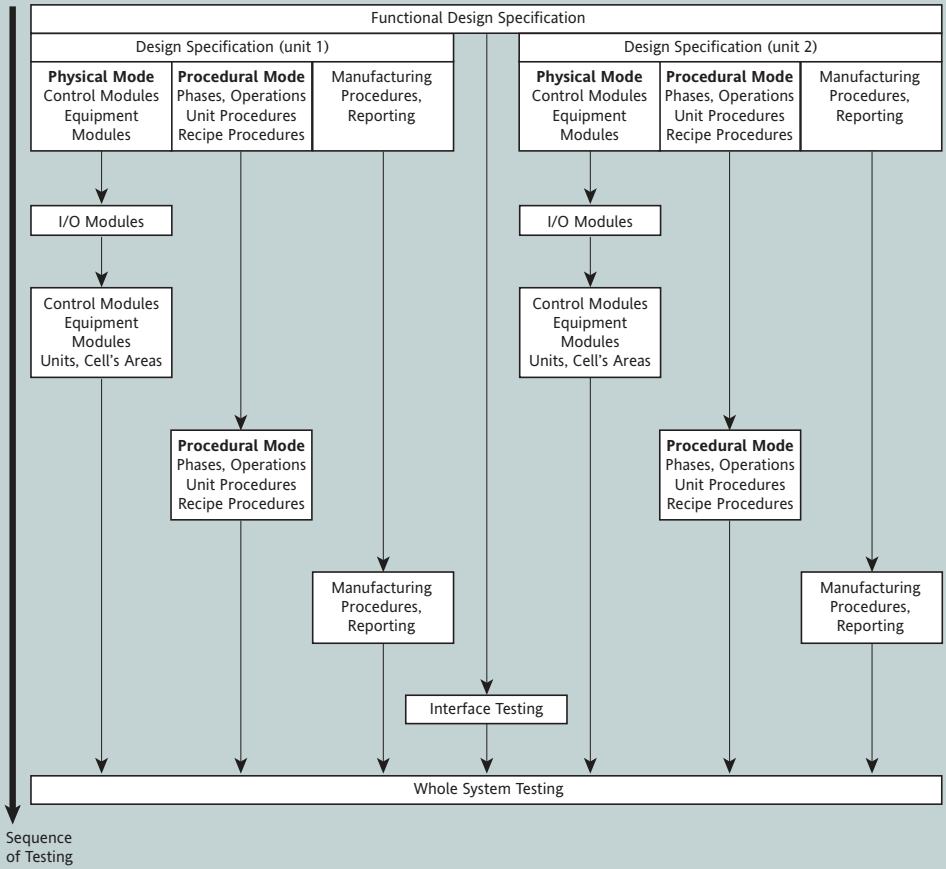
- Formal control of te test environment
- Formal record of the testers (including sample signatures)
- Calibration details for any test equipment which is required to be calibrated
- Test results recorded at the time, in ink, any errors crossed through with a single line and the change initialled and dated, no shorthand notation such as ticks, supporting prints signed and dated and referenced to the test
- Test incidents formally recorded, reviewed, actioned and closed down

The time taken to test should not be underestimated when quoting for pharmaceutical projects. As a rule of thumb, testing a system to these standards, by the time module tests, system integration tests and acceptance tests are added up, takes as long as implementing the system in the first place.

EUROTHERM® FLEXIBLE SOLUTIONS

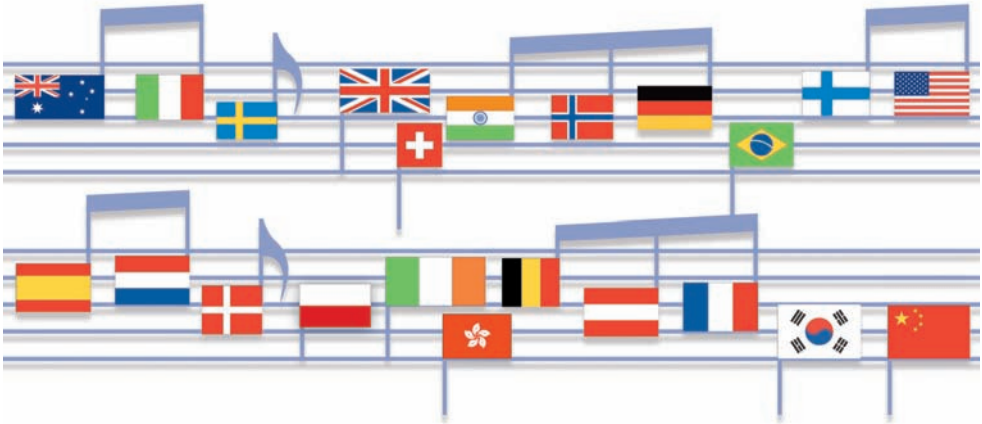
Life Sciences

Example Process Control System



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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ED56

Eurotherm is also represented in the following countries:

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Bahrain
Bangladesh
Benin
Bosnia and Herzegovina
Bulgaria
Burkina Faso
Cameroon
Canada
Czech Republic
Egypt
Georgia
Greece
Guinea-Conakry
Hungary
Indonesia
Iran
Iraq
Israel
Ivory Coast
Japan
Jordan
Kazakhstan
Kenya
Kuwait
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