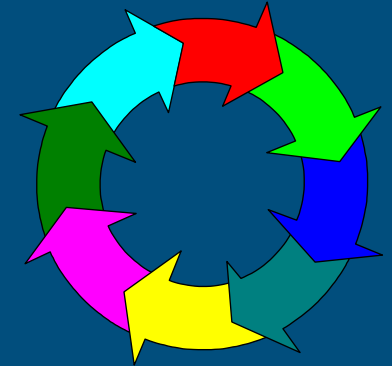


Development and Basic Concepts of GMP Requirements



GMP Course, 10 June 2004, Istanbul

Dr. Andreas Brutsche, Novartis Pharma, Switzerland

- **GMP - Development - History of Pharmaceutical Regulations**
- **Major International cGMPs : EU, US, Japan, WHO**
- **Mutual Recognition Agreements**
- **The Potential Advantage of GMP Compliance**
- **FDA - Novartis “Partnership” - Project**
- **Major cGMP Topics :**
Quality Systems, Change Control, Recall Organisation, Deviation Handling, Qualification, Validation, Development in API-GMPs

Perception of Quality Management

1900 Manufacturing Control

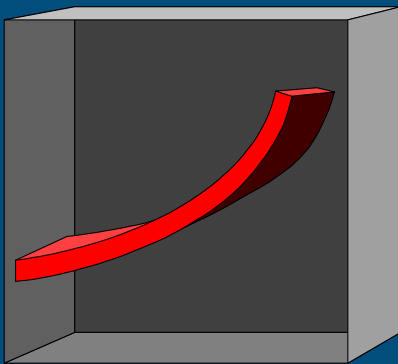
1930 Analytical Control

1960 Quality Control

1970 Good Manufacturing Practice

1977 Quality Assurance

? Quality Management ?



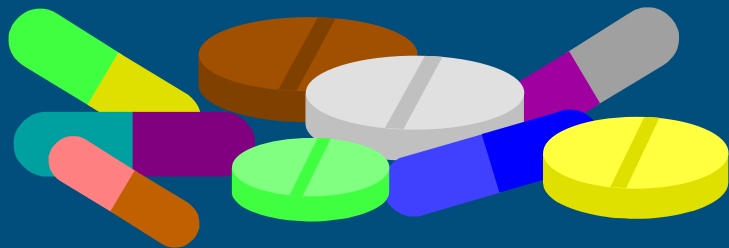
GMP Development

History of Pharmaceutical Regulation

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1906 A report on the atrocious conditions in the Chicago meat-packing industry led to the original **Food and Drug Act** in the US

1938 Sulfanilamide Elixier contaminated with diethylene glycol killed a large number of patients. This led to the **Food & Cosmetic Act**



GMP Development

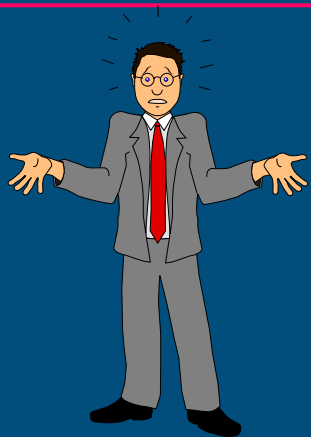
History of Pharmaceutical Regulation

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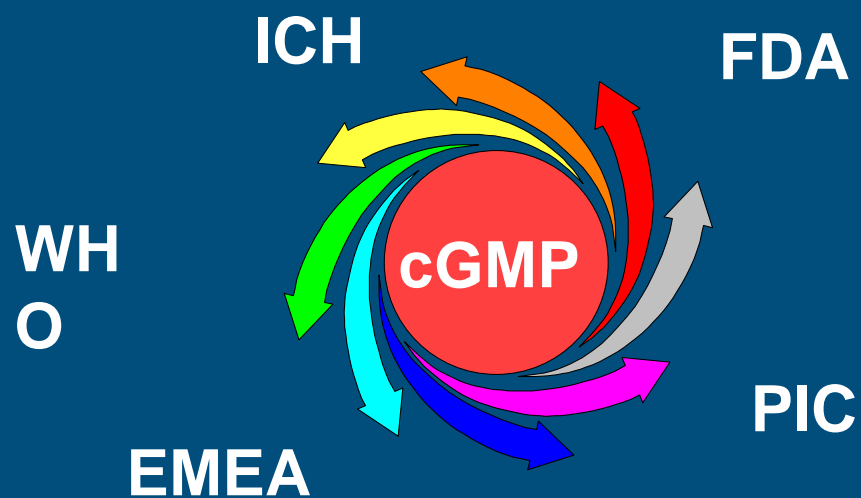
1962 Thalidomide tragedy in Europe led to a tightening up of the testing of pharmaceutical products prior to marketing. This incident prompted the **Kefauver-Harris Amendments** (enacted as **21 CFR** and the first GMPs)

1991 An incident in Nigeria, involving ethylene glycol and killing more than 100 children, that really began the push for international harmonisation

Other milestones : Contaminated blood products, TSE,
Dioxin case in Belgium (1999)



**At present
the biggest obstacle is
the definition that constitutes cGMP**



Major International cGMPs :

European Union (EMA) cGMPs

- EU GMPs are more specific than 21 CFR 211.
- EU Inspectors are spending more time looking at the equipment and the facility (e.g. cleanliness zoning) than FDA
- The EU also uses the concept of the Qualified person, who, in many cases, can be held personally liable for any deviations
- The basic GMP requirements consist of 16 articles, and are supported by 14 annexes. In a major difference from the US regulations, these GMPs are not published for comment industry, and go into great detail.

Major International cGMPs :

US (FDA)

- “FDA has driven GMP development”
- Consequences of non-compliance, which can go as far as the assessment of criminal or civil charges
- Investigators are focused on GMPs (deviation handling and failure investigation) and registration issues
- Audit technique : Document trail
- Specific GMP topics :
 - **Label reconciliation**
 - **Pre-numbered worksheets**
 - **Annual Product Review**
 - **Out of specification handling (Barr Case)**
 - **etc.**

Japan

- As might be expected, the cultural differences between east and west are reflected in the Japanese GMPs
- The Japanese culture places a great deal of importance on visual aspects (therefore most Pharmaceutical companies make a 100% visual inspection of all batches shipped to Japan)
- Concept of respect for the individual
- Those following US or EU GMPs would have no problem surmounting the requirements of the Japanese GMPs

Major International cGMPs :

World Health Organisation

- The first WHO GMPs for Pharmaceutical Products were drafted 1967. These were revised in 1968, 1971, and, most recently, 1992.
- These GMPs call for very comprehensive documentation, and were designed to support WHO certification scheme.
- WHO requirements focus more on Quality Assurance throughout the manufacturing process, rather than just testing at the end.
- WHO`s requirements for Good Manufacturing Practices are simply a guide as the Agency has no inspectional body

Mutual Recognition Agreements (MRAs)

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Mutual Recognition Agreements are essential to avoid multiple inspections, which are becoming a major problem for manufacturers

MRAs can avoid:

- Costly re-analysis of imported products
- Have the potential to promote GMP harmonisation

Stumble points to such agreements include standards equivalence and national inspection system

The potential advantages of GMP Compliance

The attainment of GMP Compliance within a manufacturing operation benefits:

- Delivery performance by eliminating wasteful practices
- Increasing productivity
- Providing a higher level of assurance of quality at every manufacturing and packaging stage

The rewards of this approach are:

- Greater operational efficiencies
- Lower costs
- Improved reputation and competitiveness

The Pharmaceutical Market and the Authorities

The regulatory authorities require medicines which provide:

High standards of Quality Assurance

The purchasing authorities also require medicines which will provide both high standards of Quality and:

Value for money when purchased

There is a careful balance to be struck between **Quality** and **Value**

FDA - Novartis “Partnership” - Project

Sterile manufacturing facility, Building 303, Stein, Switzerland

General Goals :

- Basis: FMD No.135
- Proactive relationship with FDA
- Prevent costly construction errors
- Increase efficiency and result in the timely processing of applications
- Avoid duplication of review
- Co-ordination of reviews with project milestones
- Co-ordination with regulatory affairs (Novartis)

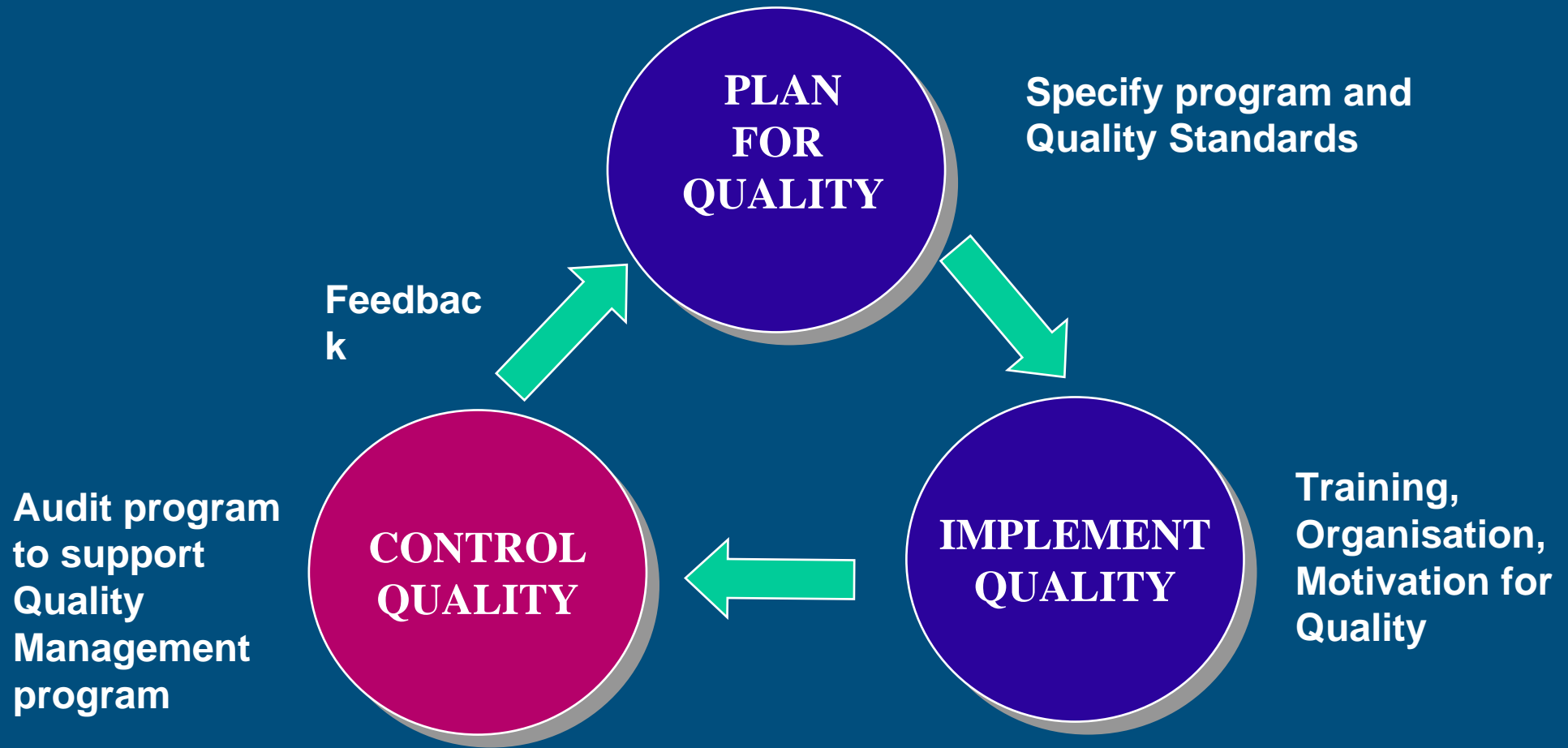
FDA - Novartis “Partnership” - Project

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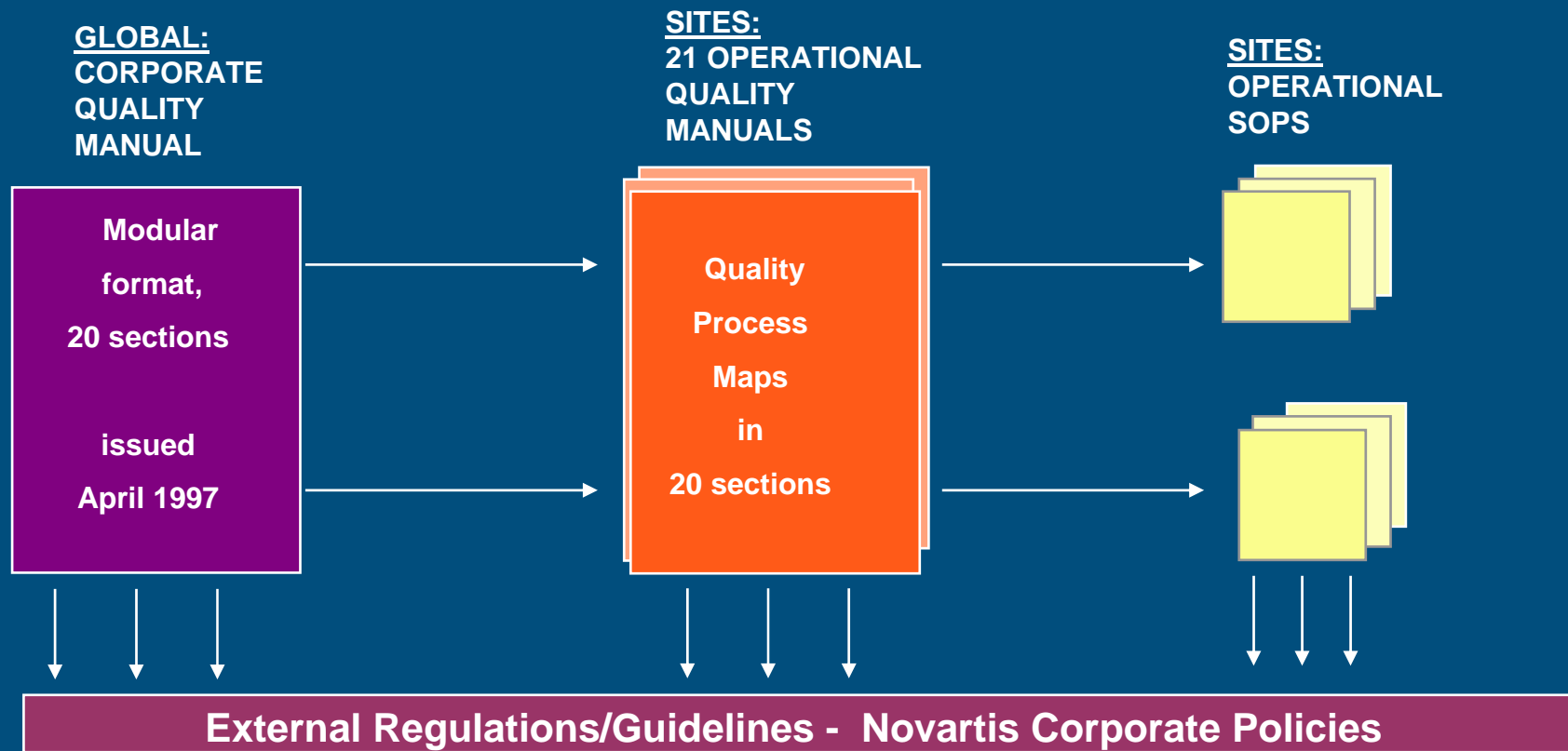
- **FDA Reviews:**

- Offers to Novartis best opinion at the time on compliance with cGMPs
- Offers FDA to become involved in construction details and new technologies (isolators)
- Serves the objectives of FDA`s overall compliance and regulatory policies

The Global Novartis Quality System



Global Quality System: *Operational Quality Manuals*



Each site is required to produce an operational quality manual, based on the corporate manual, and including maps of key quality processes, with cross reference to operational SOPs.

This provides an overview of quality systems on site, and the basis for process re-engineering/SOP simplification (Corporate Project).

Qualification, Validation, Calibration

Validation Iceberg

Visible Process

Unvalidated Process



Equipment Qualification

- User Requirement Specifications (URS)
 - Design Qualification
 - Conceptual Design
 - Basic Design
 - Detail Design
 - Installation Qualification
 - Operational Qualification
 - Performance Qualification
- ➔ Calibration and Maintenance Programs
- ➔ Retrospective Qualification



Process Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its **predetermined specifications** and **quality attributes**.





Development / Pilot Batches

- Identify critical parameters
- Set specifications
- Establish operating ranges



Full Scale Demo Batches

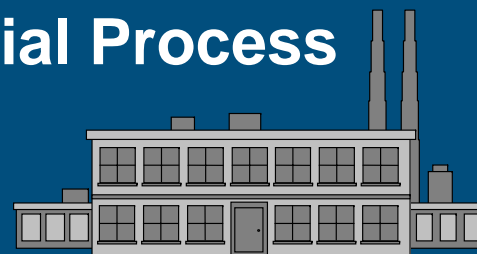


Validation Protocol



Validation : Commercial Process

Process Validation



Process Validation Requirements

Summary

- **Identify Critical Process Parameters
(Risk Assessment)**
- **Establish Appropriate Specifications**
- **Develop a Rugged Process with Specific Manufacturing Procedures**
- **Good Documentation**
- **Process Change Control System**
- **Training & Responsibilities**



Cleaning Validation

- The important benefit from conducting cleaning validation work is the identification and correction of potential problems, previously unsuspected, which could compromise the safety, efficacy, or quality of subsequent batches of drug product produced with the equipment
- Several serious problems can be prevented through the use of a reasonable cleaning validation program:
 - **Cross-contamination with active ingredients**
 - **Contamination with unintended materials or compounds**
 - **Contamination with cleaning agents**
 - **Microbiological contamination**



Cleaning Validation

- Prerequisite : challenged cleaning procedure
- Manual cleaning versus automated cleaning
- Introduction of a matrix approach to identify worst case
- Sampling procedure (final rinse, swab samples)
- Acceptance criteria :
 - **Visually clean criteria**
 - **10 ppm criteria**
 - **Dosage criteria**
- **Cleaning validation for mono-purpose equipment**

Complaint Handling / Recall Organisation

Even with the best Quality Assurance System there is no 100% security in the manufacturing of pharmaceutical products, because of:

- Human errors
- Technical errors

Therefore an excellent complaint handling system / recall system should be in place.

Complaint Handling

Every Pharma country organisation must have written systems that :

- **Service and respond to all customer complaints in a timely and helpful manner**
- **Identify and distinguish medical complaints and product tampering, from other complaints**
- **Document the exchange / communication with the customer**
- **Relay information immediately to the relevant manufacturing site or reporting unit**
- **Assess and take action regarding the relevance of the complaint (e.g. influence to other batches or products)**

Complaint Handling

- A complaint may lead to a product recall, therefore it requires immediate investigation with first priority by all departments concerned
- All Manufacturing sites must have systems to:
 - **Record the information and take appropriate follow-up action, including, as necessary, notification of regulatory authorities / notified bodies pursuant to local regulations and approval requirements**
 - **Perform trend analysis, failure investigation and corrective action (product recall, withdrawal, etc.)**
- Any immediate or short/mid/long term corrective measure decided as a result of the investigation of a complaint should be documented and followed up for completion and effectiveness

Recall Organisation

Classification of Recalls

- **Class I:** There is a reasonable probability that the use of, or exposure to, a defective product will cause serious adverse health consequences or death
- **Class II:** Use of, or exposure to, a defective product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
- **Class III:** Use of, or exposure to, a defective product is not likely to cause adverse health consequences

- **Change** is necessary - but uncontrolled change is dangerous
- In a complex, interactive manufacturing situation, **changes** made in one part of the organisation can have a profound effect on another part of the operation.
- **Change** control is an essential feature of any Quality Assurance System to ensure the effects of change are fully evaluated before implementation.
- **Change** control is a requirement to ensure that all parts of the organisation remain in continuous compliance with current licensing documentation.
- **Change** control ensures that changes made at the operational level are notified to the Authorities if appropriate.

Purpose of Change Control

- **Traceability**
- **Maintenance of regulatory compliance status**
- **Maintenance of validated status**
- **Co-ordination of internal measures to ensure smooth implementation of desirable or necessary changes**

Change Control: **Traceability**

Who made the change

Why was the change necessary

When was the change implemented

What internal consequences arise :

- Risk / benefit assessment
- Cost / benefit assessment
- Regulatory impact

Who gave approvals



Contracts

Contracts for contract manufacture and analysis :

- There must be a formally agreed, written contract agreement covering the manufacture, packaging and Control / Quality Assurance activities arranged under contract and any technical arrangements made in connection with it applied.
- Prior to any contract agreement signature, audit of the facilities must be undertaken by QA to ensure that the operation is in compliance with cGMP standards. A report must be available

Documentation and Records Control

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General Requirements

- Good documentation constitutes an essential part of Quality Assurance. Clearly written documentation prevents errors from spoken communication and permits tracing of information.
- Documents must be designed, prepared, reviewed and distributed with care.
- Documents must be approved, designed and dated by appropriate, competent and authorised persons.
- Documents must be regularly reviewed and kept up-to-date.
- Any correction made to a document must be signed or initialled and dated.

- **Electronic Records - Controls**

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 disclaim the signed record as not genuine.

- **Electronic Signatures - General Requirements**

Each electronic signature must be unique to one individual and shall not be reused by, or resigned to, anyone else. Electronic signature must either be based on biometrics or have at least two distinct identification components such as an identification code and password.

Supplier Approval, Qualification for reduced Testing, and Monitoring

35

- The purchase of materials and products is an important operation which must involve staff who have a particular and thorough knowledge of suppliers
- Materials and products must only be purchased from suppliers approved by QA. Whenever possible the material must be purchased directly from the producer
- Supplier Qualification Process : **Approved, qualified, certified suppliers**
- Exceptions for Material Supplied from other Novartis sites
 - Novartis sites are governed by the Novartis quality management system and are routinely audited to these standards.
 - Novartis sites are automatically approved for reduced testing.

Important GMP Features

- Product Identification and Traceability
- Inspection and Test Status - Material Identification
- Batch Record Review and Release Decision
- Corrective and preventative Action
- Receipt, Storage, Handling and Distribution of Materials and Products
- Archiving
- Quality Audits
- Qualification and Training of Personnel
- Cleanliness Zoning

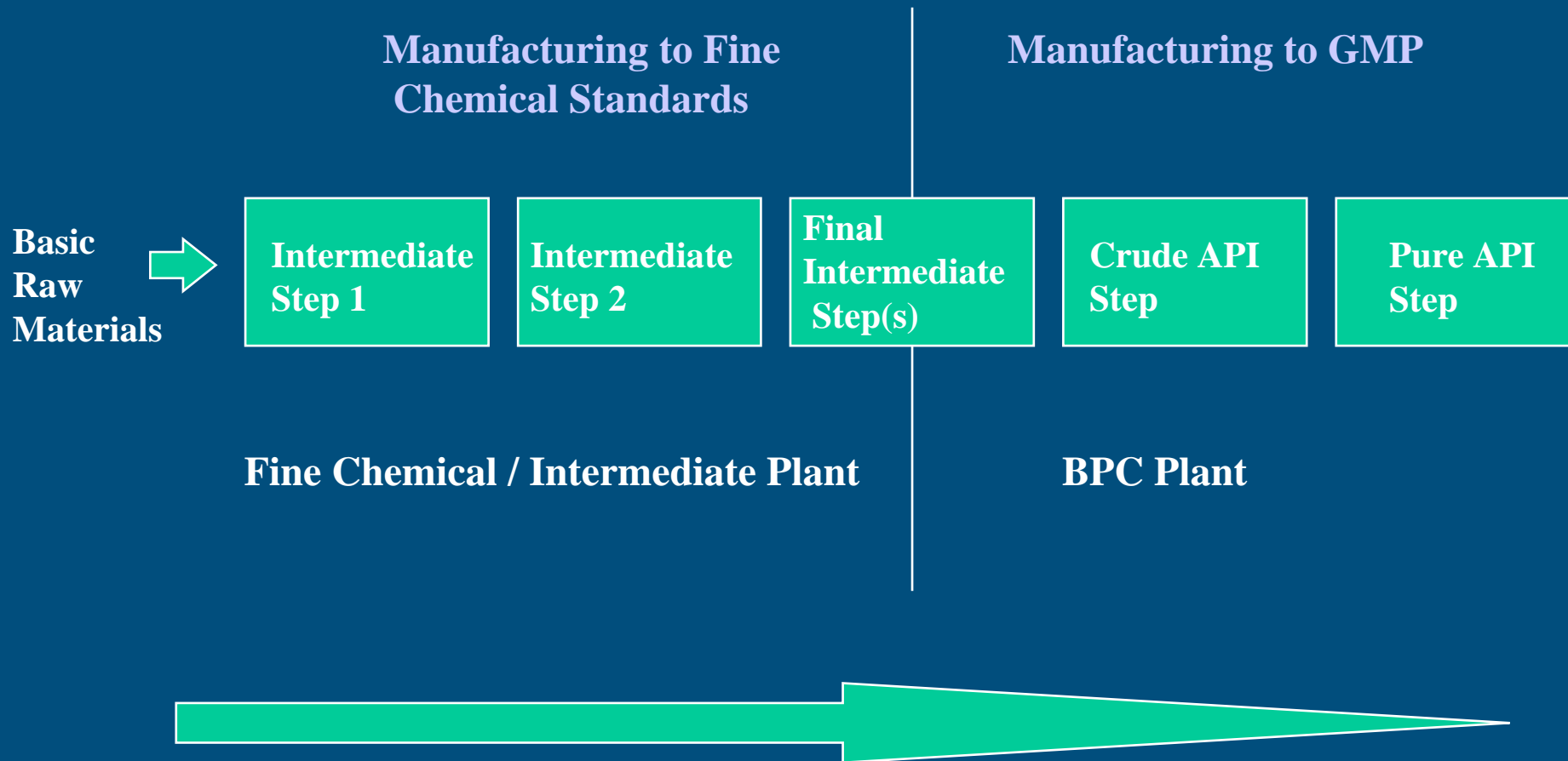
Control of non-conforming Product

- Non -conforming product is material which fails on testing to meet determined specification or has been manufactured using an unauthorised or deviating process.
- Failure Investigation / Out of Specification Handling
- Non-conforming material can be handled as follows :
 - It can be rejected and destroyed according to local procedures for handling of waste material.
 - It can be re-processed according to the existing procedure for processing.
 - It can be re-worked according to a new procedure which usually has to be developed for the material which does not conform.

Development in API GMPs

- **Classification of Active Pharmaceutical Ingredients :**
 - **Non sterile active ingredients going into non sterile products**
 - **Non sterile active ingredients going into sterile products**
 - **Sterile active ingredients**
- **Cleanliness Zoning**
- **Key intermediate concept for validation**
- **Water quality for the various steps**
- **Recovered solvents**
- **GMP strategies**

Status of Active Pharmaceutical Ingredients (APIs)



GMP
versus
Innovation
(?)



The **approved** and not the **best**

- **Technology**

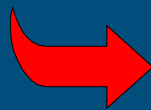
- **Manufacturing Process**

- **Analytical Method**

is in compliance with cGMP requirements

GMP is more than :

G



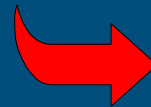
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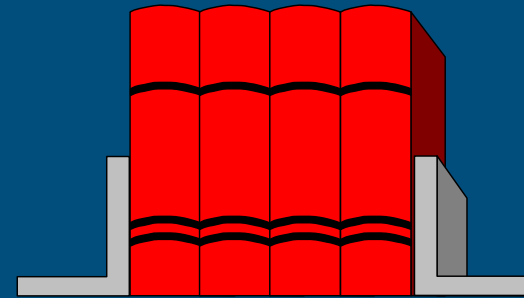


More

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Paper



GMP
Standard

