



Regulatory: New Trends and Requirements for Starting Materials in Biopharm Production

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Content



- Biopharmaceutical Background / General Points
- GMP: Manufacturing / Safety
- Starting Materials (SMs)
- Regulatory Requirements Biopharm
- Raw Materials in Pharmaceutical Production
- Regulatory Support

General Points



- Biotechnology-derived pharmaceuticals (biopharmaceuticals):
 - initial developments in the **early 1980's**
 - **first marketing authorisations**: granted later **in that decade**
- Major issue: **Safety assessment** of these products
Several **guidelines** and **points-to-consider** documents have been issued by various regulatory agencies
- Ongoing review of documents
 - provides **useful background** in developing (**manufacturing**) new biopharmaceuticals

Definition BIOPHARM

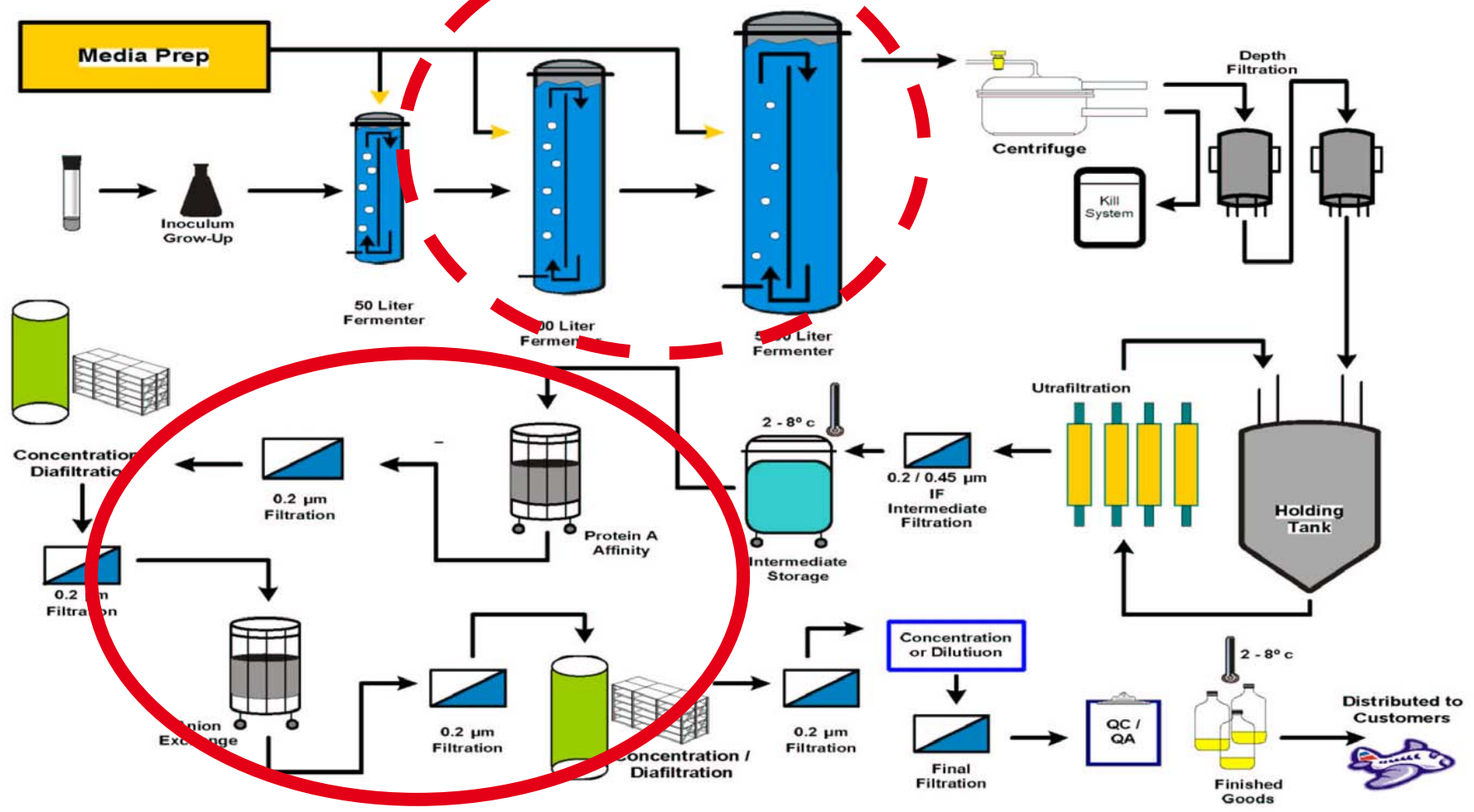


- **Biotech:** defines a way of producing substances
 - Use of fermentation processes
 - Use for numerous types of products in many market segments (e.g. vitamins, agrochemicals, DHA and many more)
- **BioPharm:** defines a market segment where biotechnological processes are used
 - Manufacturing of pharmaceutically active substances
 - e.g. monoclonal antibodies, recombinant proteins, vaccines, oligonucleotides, blood products
 - Via cell culture of mammalian cells
 - Use of sophisticated downstream processes for isolation and purification

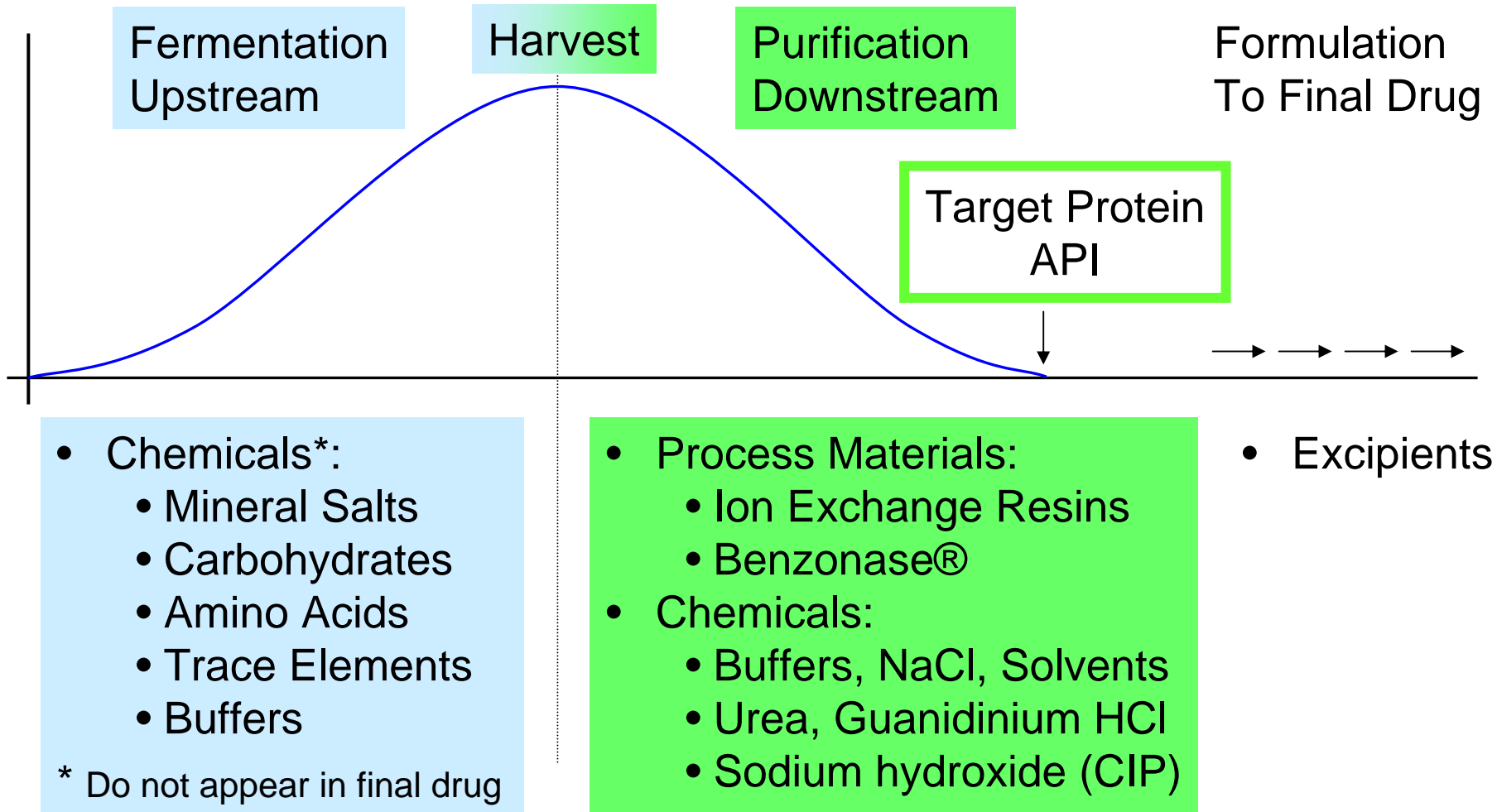
5000 Litre Process for Protein Production from Mammalian Cells



(J. Birch, Speciality Chemicals Magazine, April 2003)



Biopharmaceutical Process



Chemical reaction → Purification → Crystallisation → Drying → Excipient
API

- **Chemicals**

the whole range of organic and inorganic chemical products for chemical reaction and synthesis

Formulation of Final Drug



Mixing → Granulation → Tableting → Coating → Solid Drug

Mixing → Filtration → Filling → Liquid Drug

- **Excipients**

- solvents/ co-solvents
- gel forming agents
- antioxidants
- lubricants /flow regulators
- essential oils and flavours
- vitamins
- buffers
- polyols
- preservatives
- dyes and pigments
- minerals

- **APIs**

- Magnesium chloride
- Calcium chloride
- Target Protein
- etc...

General Points: Safety



- Appropriate controls at all stages of manufacture to assure the quality of the API/Intermediate
 - Depending upon the
 - Source
 - Method of preparation
 - Intended use of the API
 - Appropriate equipment
 - Environmental controls
 - Where appropriate, the removal of media components, host cell proteins and other process related impurities should be demonstrated
- Control of bio burden
- Viral contamination and/or endotoxins during manufacturing
- Monitoring of process at key stages
- Minimise any risk of contamination

- Unlike **conventional pharmaceutical** products produced by chemical and physical techniques capable of a **high level of consistency**, **biopharmaceuticals** involve biological processes and materials such as cultivation of cells or material extraction from living cells.

 *Use of living cells needs additional precautions*

- Safety concerns may arise from the presence of impurities or contaminants.
 - **Important focus:**
Establish a purification processes to remove impurities and contaminants

 **Sufficiently characterized** products to allow an appropriate design of **preclinical safety studies**

- Although GMP requirements are similar to those applied to conventional pharmaceuticals extra precautions must be applied to all persons concerned with the manufacturing process (including maintenance)
- There are potential risks associated with host cell contaminants derived from bacteria, yeast, plants, and mammalian cells etc.
- Additional GMP and safety training must be given to personnel regarding specific products and their handling

Regulations: General points



There are few specific and defined requirements for APIs manufactured by cell culture/fermentation:

Section 18 of ICH Q7 covers this subject, specifically:

- 18.1 General Points
- 18.2 Cell Bank Maintenance and Record Keeping
- 18.3 Cell Culture/Fermentation
- 18.4 Harvesting, Isolation and Purification
- 18.5 Viral removal/Inactivation steps

Section 18 does not stand alone

- General GMP requirements and Section 7 of ICH Q7 still apply

Starting Materials (SMs)



- The **source of SMs** must be clearly defined and specified
- Where **QC testing is lengthy**, the **processing of SMs** is **possible** before the test results are made available
- Where **sterilised SMs** are required, the preferred method of sterilisation **is heat**
- SMs that are purchased “sterilised” **MUST NOT** be subject to a reduced testing regime

Starting Materials



- It should exist **written procedures** for supplier **qualification**
- Manufacture should have **qualified** and **competent** suppliers (audit, questionnaires)
- Preferably should be used pharmaceutical grade product
- Preferable needed **certificates** are (TSE/BSE, GMO, Allergene, Aflatoxin, Halal, Kosher)
- **Customized solution** on QC testing and regulatory documentations
- If possible **no animal derived materials** (TSE/BSE, cross-contamination)

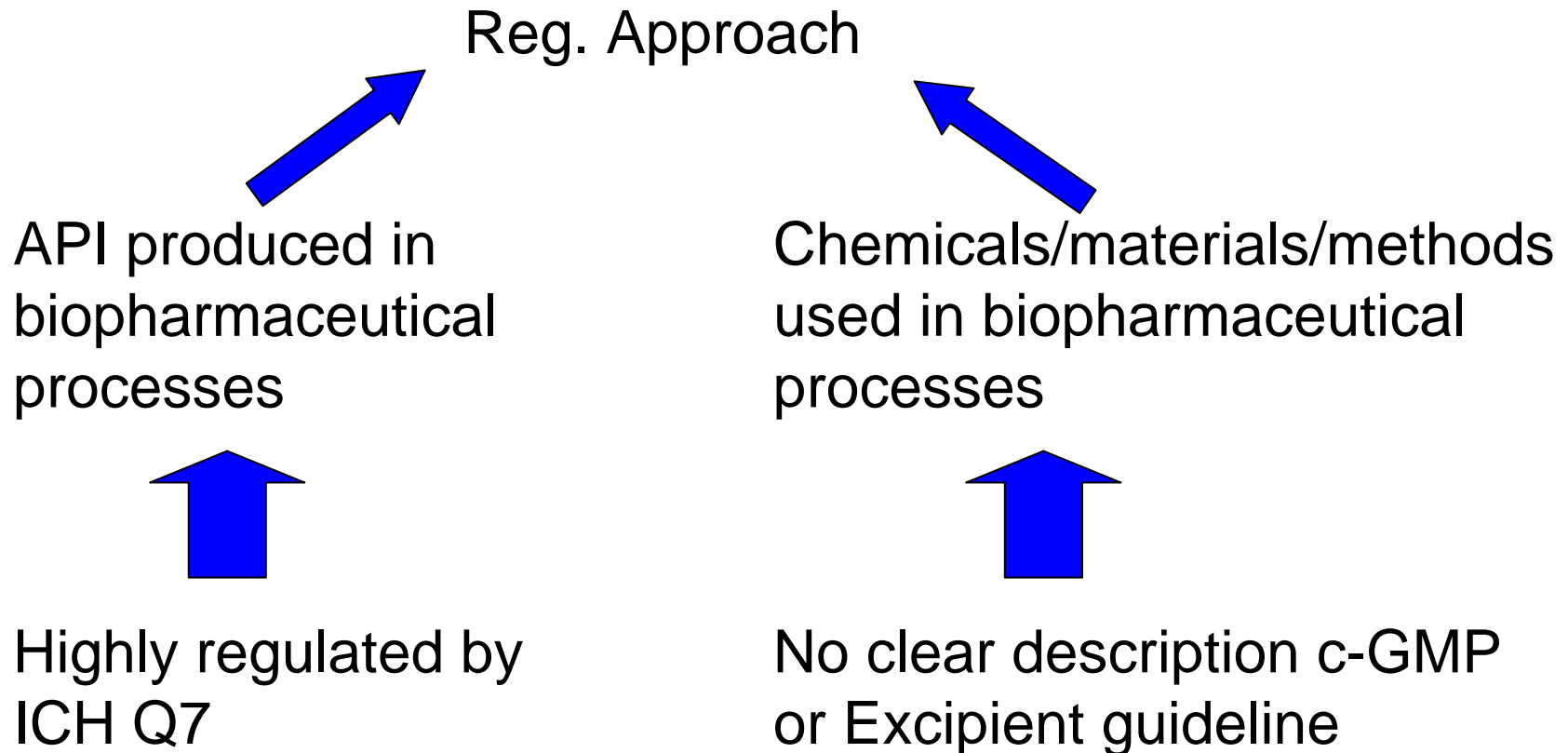
Starting Materials



- Comprehensive **change agreement** are required from the suppliers
 - **Specification**
 - Transfer of the **manufacturing site**
 - Change in the **agreed specification** (if not due to compendial changes)
 - Change in the **route of synthesis**
 - Change in the **nature** of the SMs (BSE/TSE-Status)

Preferably, all the listed changes should be **pre-approved**

Biopharmaceutical process



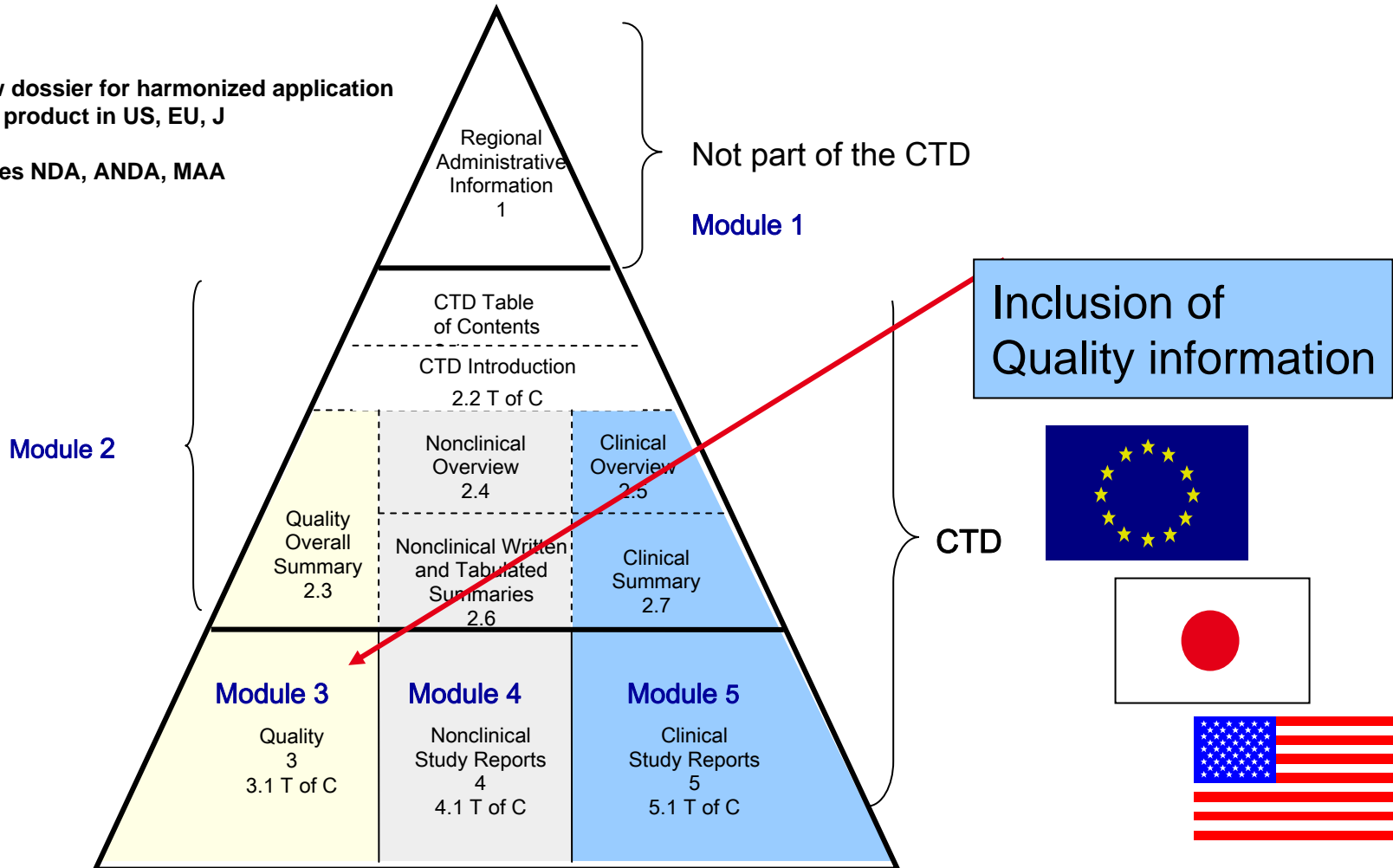


Regulatory, CTD



CTD: new dossier for harmonized application of a drug product in US, EU, J

Substitutes NDA, ANDA, MAA



- Regulatory **standards** for biotechnology-derived pharmaceuticals are in the process of harmonization among the European Union, Japan, and the United States
- All three regions have adopted a **flexible, case-by-case, science-based** approach to **preclinical safety evaluation** needed to **support clinical development** and **marketing authorization**.

- With biopharmaceutical products, the **manufacturing process** is part of the patent and is **subject to regulatory approval**
- **Process changes** trigger the need for **new clinical trials**, yielding greater development **costs**
- FDA's Center for Biologics Evaluation Research (**CBER**) has **developed draft guidelines** for a post approval comparability protocol allowing companies **to combine** several **manufacturing changes** into a single abbreviated post approval application when they change their process
- Companies are not **required** to **duplicate clinical studies** after a drug manufacturing **change**, if they can show that it is **bio-equivalent** and causes **no new adverse reaction**

Regulations and Guidelines for Biotechnological Products (Examples)



- ICH Guidelines

- ICH Q7 GMP for Active Pharmaceutical Ingredients (chapter 18)
- ICH Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnological/Biological Products Derived from Cell Lines of Human or Animal Origin
- ICH Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- ICH Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
- ICH Q5E Quality of Biotechnological Products: Comparability of Biotechnological/Biological Products Subjected to Changes in their Manufacturing Process
- ICH Q6B Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Regulations and Guidelines for Biotechnological Products (Examples)



- FDA Guidance Documents

- Bioanalytical Method Validation
- Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals (Draft)
- Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products
- Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information
- FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

- FDA Guide to inspections

- Biotechnology Inspection Guide (11/91)

Regulations and Guidelines for Biotechnological Products (Examples)



- EMEA Guidelines

- Guideline on Similar Biological Medicinal Products
- Guideline on the Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues
- Guideline on the Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues
- Special guidelines for recombinant Human Insulin, Somatropin, GCSF and Erythropoetin
- Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and related Products
EMA/CHMP/BWP/157653/2007 coming into effect July 1st. 2009

Regulations and Guidelines for Biotechnological Products (Examples)



- EC Regulations
 - EUDRALEX Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice
 - Part II “Basic Requirements for Active Substances used as Starting Materials”
 - ANNEX 2 „Manufacture of Biological Medicinal Products for Human Use”

Regulations and Guidelines for Biotechnological Products (Examples)



- PIC/S
 - Aide-mémoire „Inspection of Biotechnology Manufactures“
- German guidance documents
 - Aide mémoire 07121002 „ Aide mémoire Bio- und Gentechnologie“

Raw Materials for Pharmaceutical Production



Process Materials

Materials used in the **production process** e.g. for purification purposes, which **do not remain in the final product**.

Excipients

Any **component** included in a **drug delivery system** other than the claimed therapeutic ingredients .

Active Pharmaceutical Ingredients (API)

Component(s) of a **finished dosage form** with a **pharmacological** activity / **therapeutic** effect.

GMP Requirements



Process Materials

DIN ISO 9001:2000
plus several
GMP requirements
derived from their
use in pharma-
ceutical
manufacturing
processes.

No specific legal
requirement

Excipients

IPEC PQG Guide
USP <1078>
„Certain
Excipients“?
Ph. Eur. requires
an adequate
quality system

Requirements
under development

APIs

WHO GMP Guide
ICH Q7
EU GMP Guide
Part II
2001/83/EC
amended by
2004/27/EC
21 CFR 210 + 211

Strictly regulated

Who defines ...

★ ... a Process Material as Process Material?

Final Drug Manufacturer defines the quality criteria for process materials according to his process.

★ ... an Excipient as Excipient ?

Final Drug Manufacturer defines the intended uses as API or Excipients

★ ... an API as API ?

Manufacturer ↔ Supplier
Intensive co-operation and communication is needed.
(2001/83/EC amended by 2004/27/EC)

Regulatory Support for Merck Products



Process Materials

Excipients

APIs

- Bulk Biologic Master File (BB-MF)

- Certificate of European Pharmacopoeia (CEP)

- Drug Master File (DMF/ASMF)
- CEP

Authorities

- Regulatory Support File (RSF)
- Certificates

- EMPROVE®
- Certificates

- Letter of Access
- DMF Open Part
- Certificates
- Stability Data

Customers

- Pharmacopoeia products (API, Excipients): This is the strongest regulated field. These products are sometimes also used in food applications.
 - Certificates are available: BSE, GMO, Allergens, Aflatoxins, Kosher, Halal, Residual solvent statement, GMP related Information, short manufacturing description, change information on specification and comprehensive change control agreement.
- Processing Materials:
 - Certificates are available: BSE, (GMO, Allergens, Aflatoxins, Kosher, Halal), GMP related Information, change information on specification and comprehensive change control agreement.

Creation of EMPROVE[®] for Excipients



- The EMPROVE[®]-Dossier is structured in the [CTD Module 3 Format](#)
- As in the CTD Format only basic information for excipients is required the [chapter S \(drug substance\)](#) is used as [structural element](#)
- [Quality Assurance](#) and [Regulatory Affairs](#) are familiar with the [structure](#) and the [content](#) for Drug Substance and final Drug Registration
- The dossier is a tool supplying [comprehensive data](#) and [information](#) for the qualification of pharmaceutical raw materials (Excipients)

EMPROVE® Main Benefits



More Convenience

- Product and documentation service
- Unique processing of relevant data for the documentation
- In line with the Common Technical Document part 3 Quality (CTD format)
- Ideal for worldwide product approval
- Clear dossier structure enables efficient working
- Highest possible security with Merck know-how

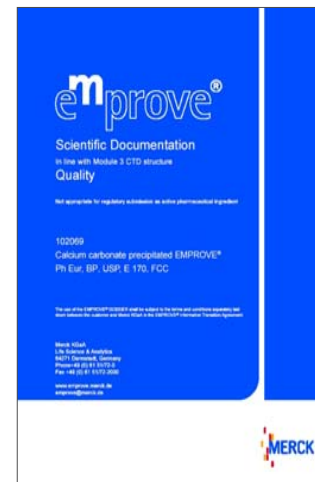


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EMPROVE® The Top Brand for Pharmaceutical Production

EMPROVE® exp
~ 150 products

Compendial

EMPROVE® bio
~ 45 products

Compendial
without stability

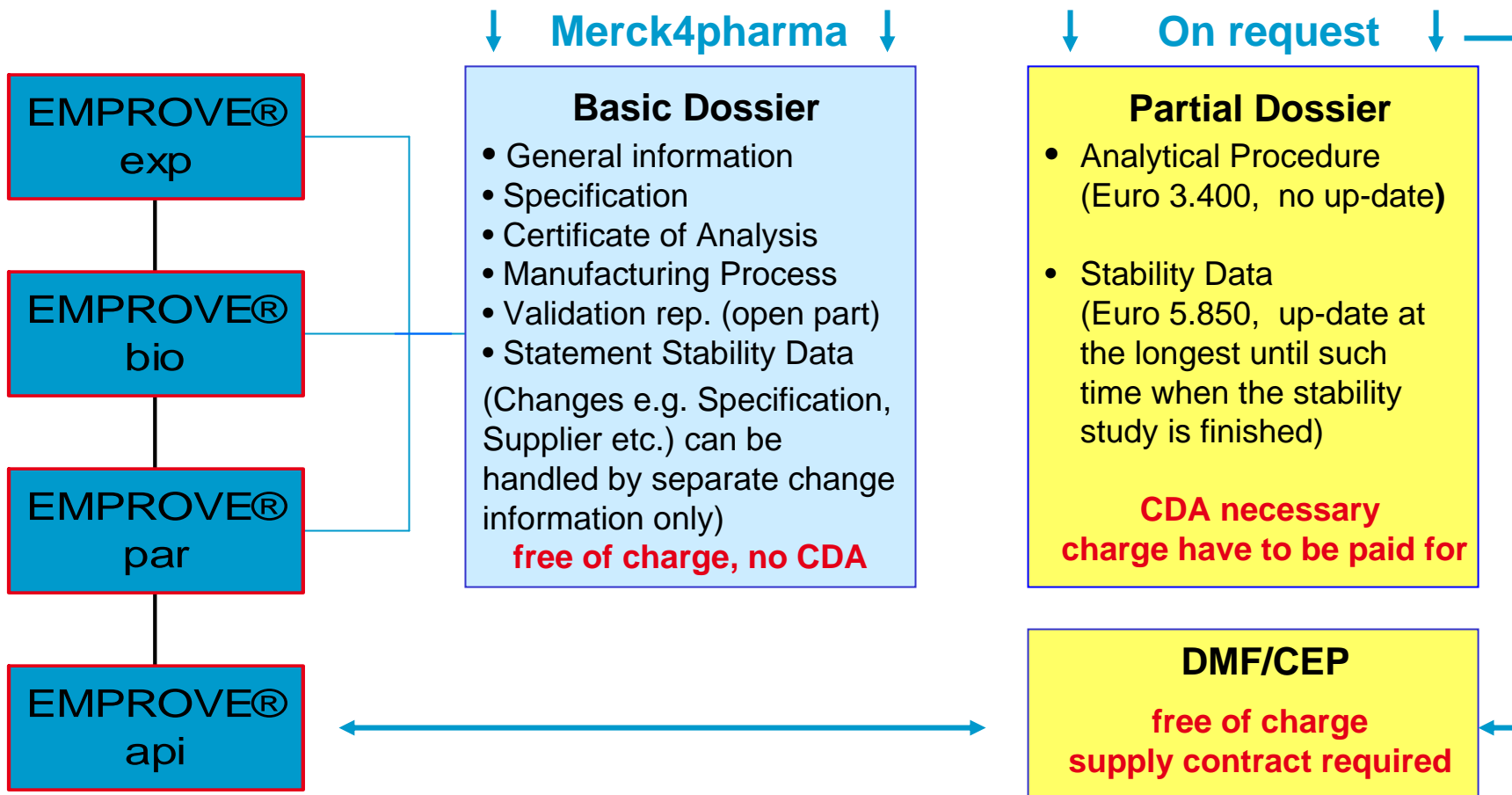
- + Endotoxines
- + Microbiology
- + partly ACS
- + partly proteases

EMPROVE® api
~ 25 products

DMF or
CEP

EMPROVE® - New Business Concept

Distribution of Dossiers



Summary



- Biopharmaceuticals are highly regulated
- Most critical point is product safety
- Different GMP Requirements for API, Excipients or Process Materials
- Appropriate documents can support the qualification and registration process
- EMPROVE® as an example for use-related Pharmaceutical Raw Material documentation