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Industrialization of pharmaceutical drug products:
Facing the regulatory challenge

1/ INTRODUCTION

2/ QUALITY STAKES

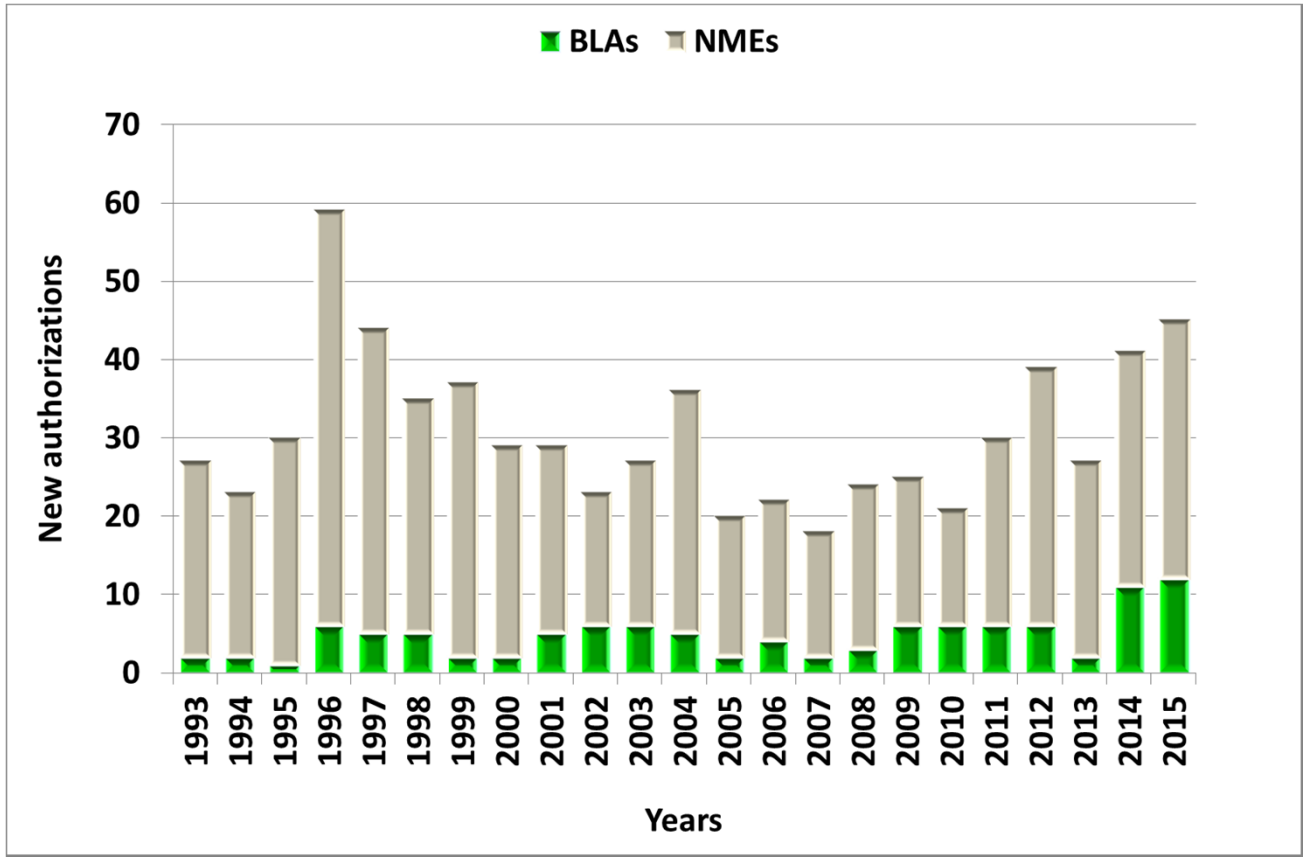
3/ REGULATORY FRAMEWORKS

4/ IMPACT ON OPERATION MANAGEMENT

5/ TREND IN PHARMACEUTICAL DEVELOPMENT

I / INTRODUCTION

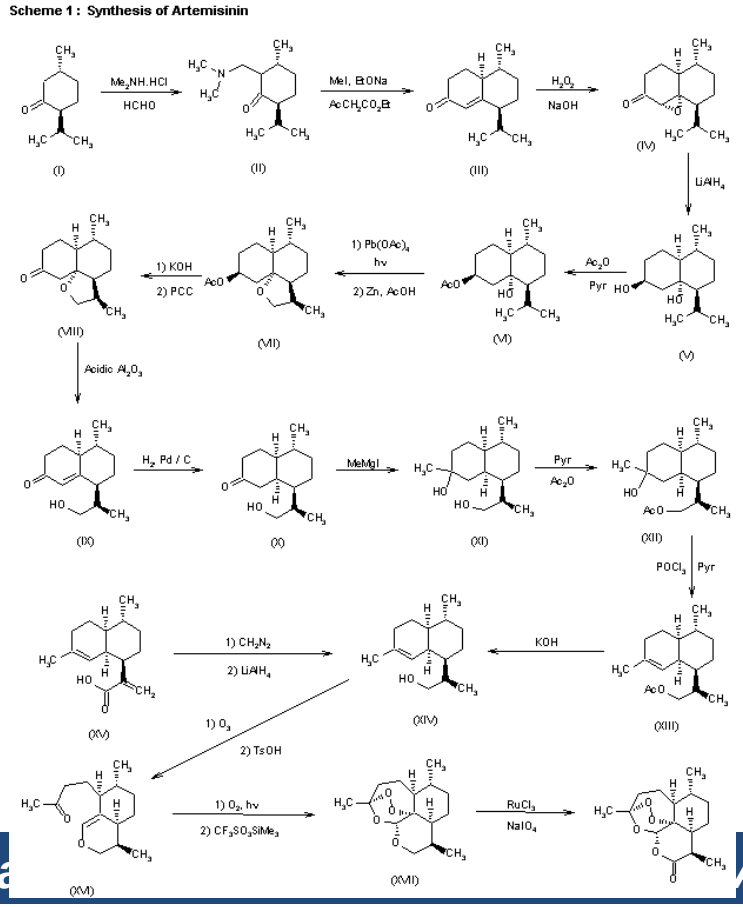
Biological product are on the rise:



Nature Reviews Drug Discovery **15, 73–76 (2016)**

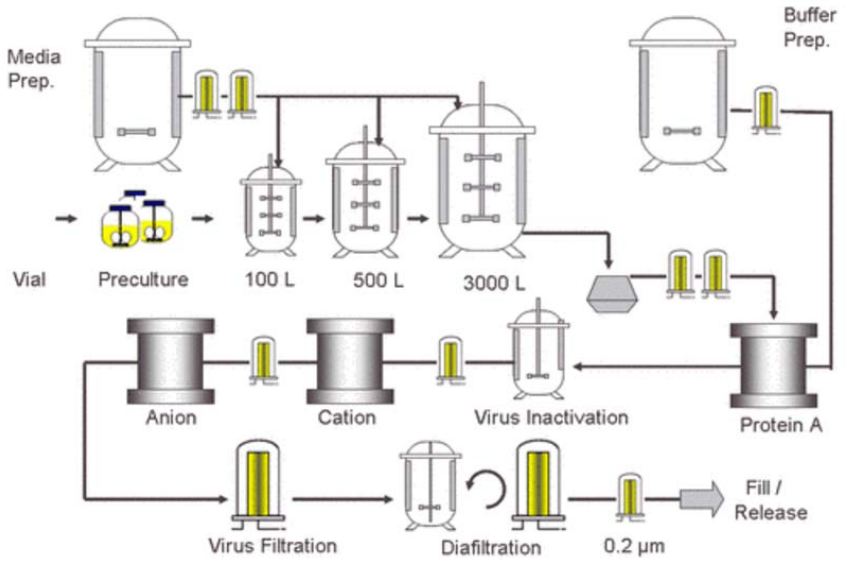
Chemical products

- Fine chemistry, long processes (>15 steps)

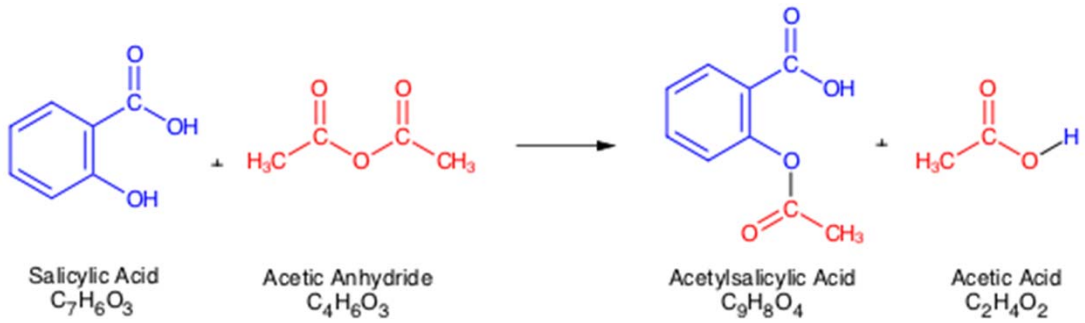


Biological products

- Biomass cultivation and fractionnation:

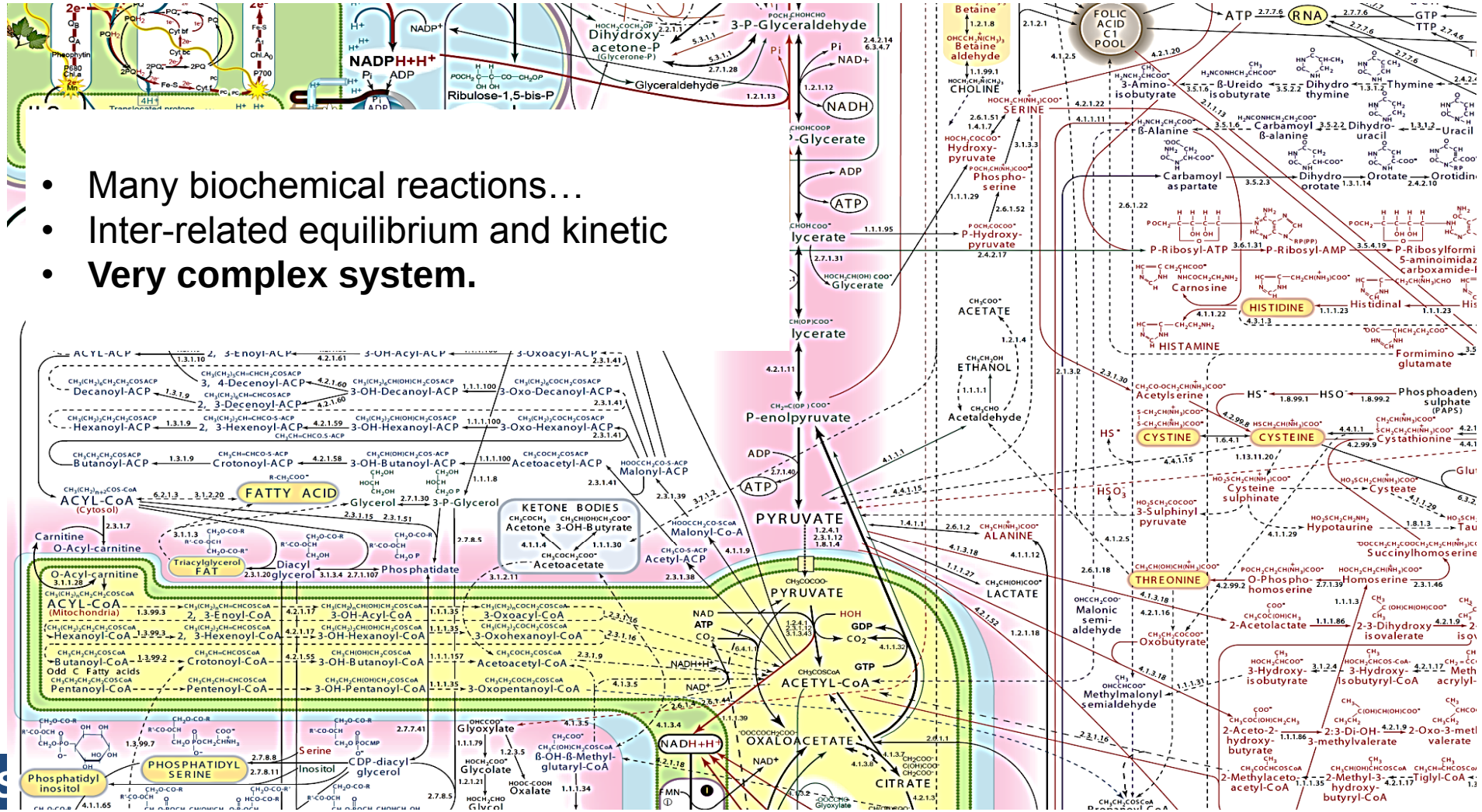


Aspirin synthesis



- Know and established reaction;
- Calculated kinetics;
- Well defined raw materials;
- Know products and impurities.

Map of metabolic patways from a plant cell:



- Many biochemical reactions…
- Inter-related equilibrium and kinetic
- **Very complex system.**

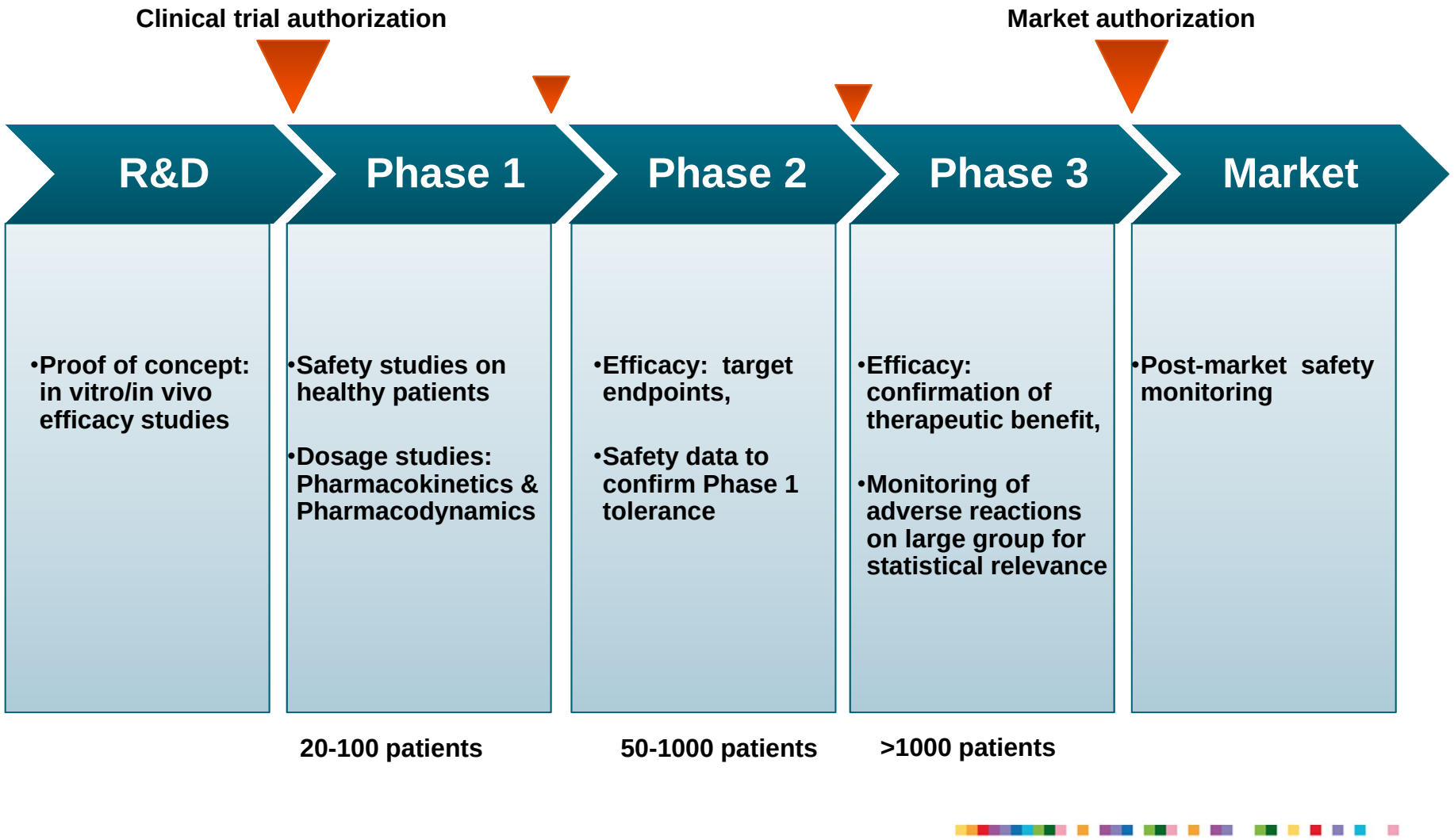
Mitigation of biological contamination during process is critical.

Operator and environment safety is important.

Biological products are often fragile and sterile.

2 / QUALITY STAKES

The process of drug development



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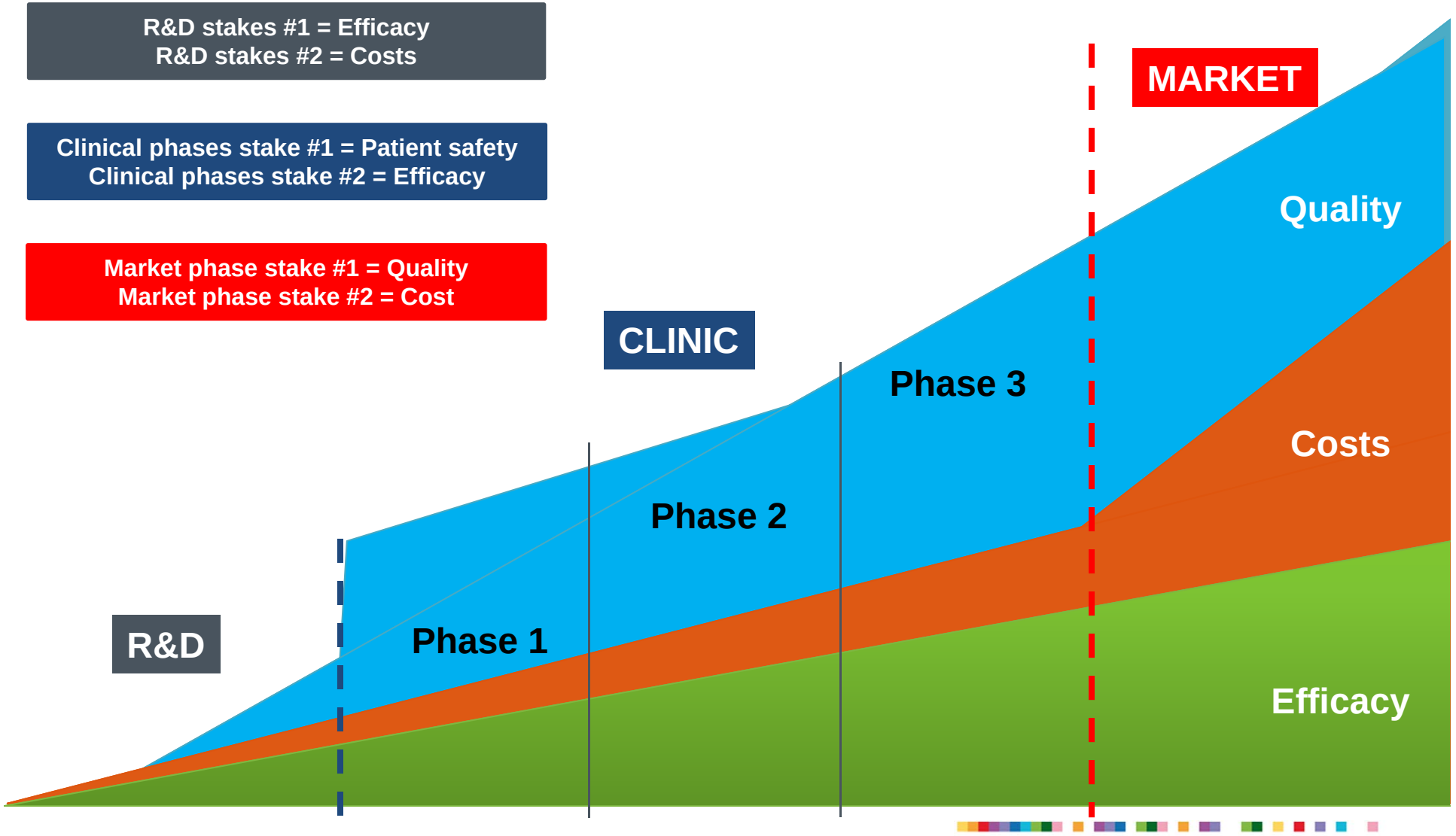
Stakes during the development of pharmaceutical products

R&D stakes #1 = Efficacy
R&D stakes #2 = Costs

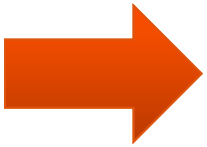
Clinical phases stake #1 = Patient safety
Clinical phases stake #2 = Efficacy

Market phase stake #1 = Quality
Market phase stake #2 = Cost



Why quality and product safety are so critical?

1. **Patients may be in bad conditions with life threatening diseases;**
2. **People may be healthy (e.g. vaccines);**
3. **Patient may suffer from chronic diseases.**
4. **Sterility of intravenous products**



The regulatory framework aims at ensuring quality consistency and product safety.

2 / REGULATORY FRAMEWORK

European Regulatory Health Authority:

European Medecines Agency http://www.ema.europa.eu/ema/

- Development of European legislation
- Evaluation of application files for new products market authorization and for clinical trials

French Regulatory Health Authority

Agence Nationale de Sécurité du Médicament et des produits de Santé

http://ansm.sante.fr/

- Development of French legislation
- inspection of pharmaceutical sites
- Integration of European Regulatory legislation

Current European regulatory legislation is issued by the European Commission:

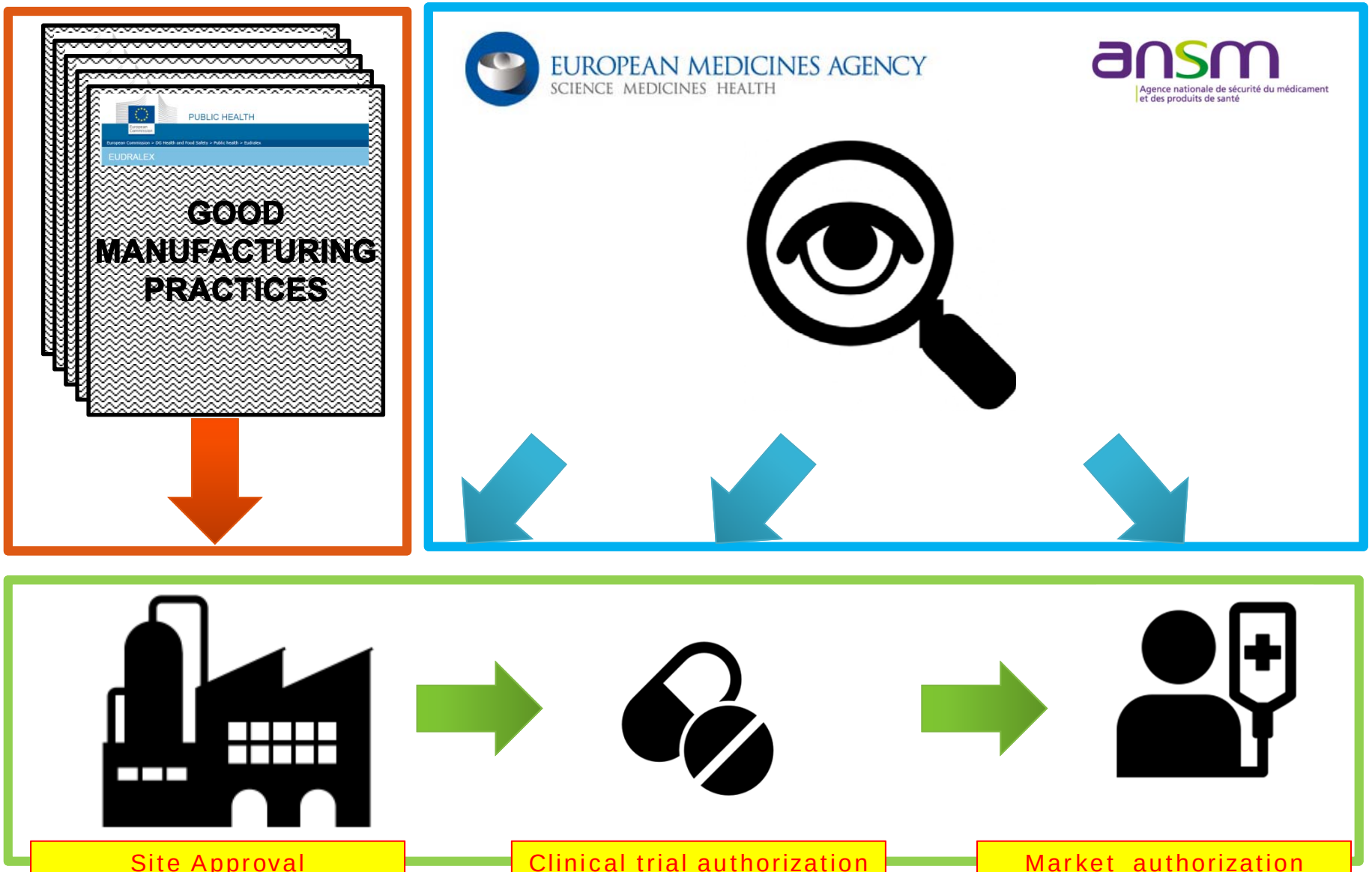
https://ec.europa.eu/health/documents/eudralex

- **Most important agencies:**
- United states: Food and Drugs Administration (FDA)
- Japan: Pharmaceuticals and Medical Devices Agency (PMDA)

- **Other important regulatory organizations:**
- World Health Organization (WHO)
- Other national agencies: China, Russia, Brazil, …

- **International relationships**
- International Conference on Harmonization (ICH)
- Brexit?
- European Trade Agreement with Canada (CETA) and US (TAFTA)

Regulatory process

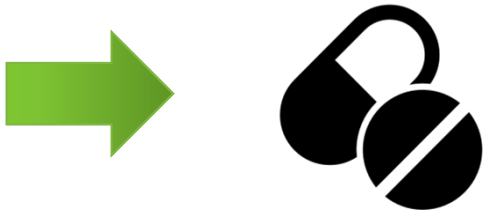


Regulatory process

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ansm
Agence nationale de sécurité du médicament et des produits de santé

Interactions is important when developing new products



Site Approval | Clinical trial authorization | Market authorization

Good Manufacturing Practices:
Overview of the requirements 1/3

- PART 1
  - **Chapter 1 – Pharmaceutical Quality System**
  - **Chapter 2 – Personnel**
  - **Chapter 3 – Premise and Equipment**
  - **Chapter 4 – Documentation**
  - **Chapter 5 – Production**
  - **Chapter 6 – Quality Control**
  - Chapter 7 – Outsourced activities
  - Chapter 8 – Complaints and Product Recall
  - Chapter 9 – Self Inspection
- PART 2
  - **Basic requirements for active substances used as starting materials***
- PART 3
  - GMP related documents

- Annexes:
  - ***Annex 1 Manufacture of Sterile Medicinal Products***
  - ***Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use***
  - Annex 3 Manufacture of Radiopharmaceuticals
  - Annex 4 Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products
  - Annex 5 Manufacture of Immunological Veterinary Medicinal Products
  - Annex 6 Manufacture of Medicinal Gases
  - Annex 7 Manufacture of Herbal Medicinal Products
  - Annex 8 Sampling of Starting and Packaging Materials
  - Annex 9 Manufacture of Liquids, Creams and Ointments
  - Annex 10 Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation

- Annexes (continued from previous slide):
  - ***Annex 11: Computerised Systems***
  - Annex 12: Use of Ionising Radiation in the Manufacture of Medicinal Products
  - ***Annex 13: Manufacture of Investigational Medicinal Products***
  - Annex 14: Manufacture of Products derived from Human Blood or Human Plasma
  - ***Annex 15: Qualification and validation***
  - Annex 16: Certification by a Qualified Person and Batch Release
  - Annex 17: Parametric Release
  - Annex 19: Reference and Retention Samples

In order to manufacture drugs in France:

- The site has to be a *pharmaceutical establishment.*
  - **The site is authorized by the French Authorities (ANSM) after submission of a file.**
  - **ANSM inspects a site prior to granting and authorization.**

- The site is under the responsibility on the *Qualified Person – Pharmacien Responsable* – who is personally and legally responsible for the pharmaceutical operation of on the site and outsourced.

Code de la santé publique R5124-X

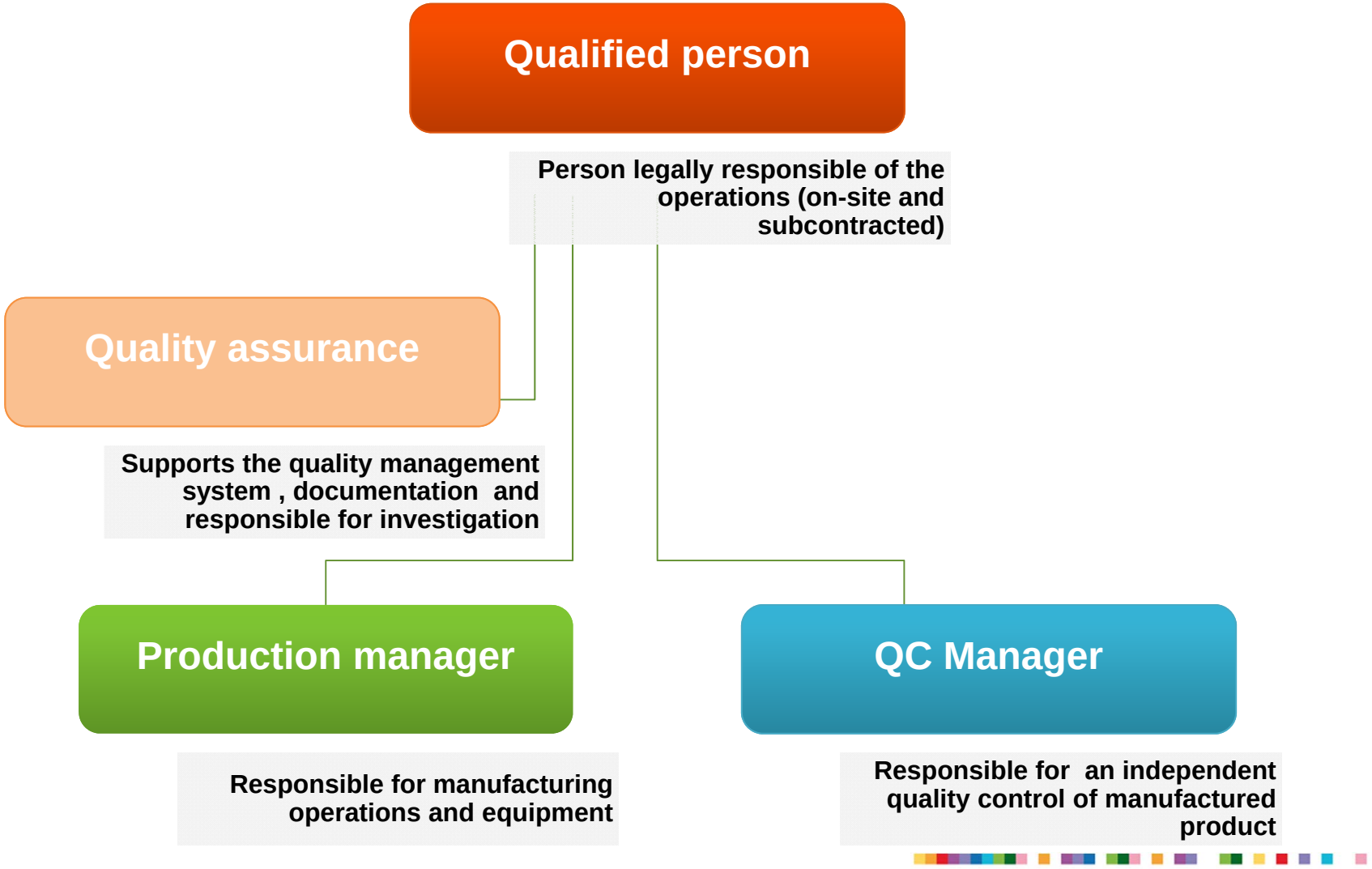
Basic requirements for active substances used as starting materials:

1. Quality Management
2. Personnel
3. Buildings and Facilities
4. Process Equipment
5. Documentation and Records
6. Materials Management
7. Production and In-Process Controls
8. Packaging and Identification Labelling of APIs and Intermediates
9. Storage and Distribution

....

4/ IMPACT ON OPERATION MANAGEMENT

Human resources
Management organization - *GMP Chap. 2*



Starting raw materials should be controlled and released:

European Pharmacopeia gathers a set of analytical assays to execute in order to confirm identity and characteristics of raw materials.

Analytical methods for product not listed in the pharmacopeia should be validated.

General methods are also described:

Example:

2.2.19. Amperometric titration

2.2.27. Thin-layer chromatography

Ex.#1: It is a common use in R&D to add fetal calf serum to the grow media:

Animal-derived products lead to biological safety concerns (TSE/BSE, viruses…)

Ex.#2: Media is commonly sterilized by autoclaving

Autoclaving modifies the nutrient profile of growth media => fertility to be verified

When scaling-up, filtration may be preferable regarding the volume of media to heat

Ex.#3: Sourcing of raw materials with sufficient traceability records for manufacturing

Qualification and Validation (1/2)
Setting-up new equipment - *GMP Annex 15*

User requirements

Functionnal specifications

Design specifications

FAT/SAT

Installation qualification

Operation qualification

Performance qualification

For clinical stage, a specific documentation(Annex 13) describes the GMP requirements.

Full validation is not required at early stage as some products may be sometimes only manufactured once at this stage.

Parameters identified and controlled should be justifiable based on knowledge available at the time.

Then, validation runs are required to ensure that the process is robust and works consistently:

A number of batches (usually 3) are repeated and compared.

Periodic re-validation is necessary.

Peremption (solution, manifolds…), storage conditions and holding times are also critical and should be considered.

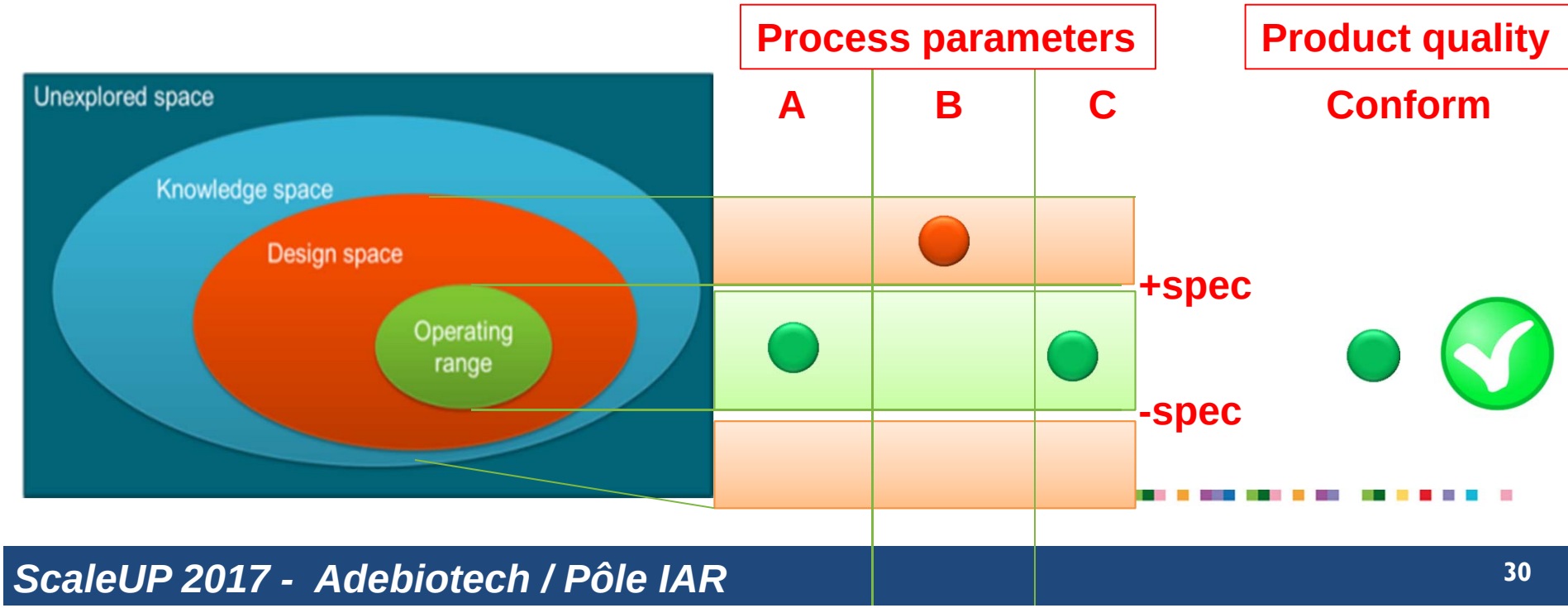
When using single-use technology, leachables and extractibles should be documented.

5/ TRENDS IN PHARMACEUTICAL DEVELOPMENT

ICH Q8: Pharmaceutical development

Define a range for process parameters which ensures that product quality attributes are always within specification limits:

1. Identification of product quality attributes
2. Identification of critical process parameters
3. Correlation of process parameters to product characteristics (DoE)
4. Operating the process within a given range to ensure quality of the product



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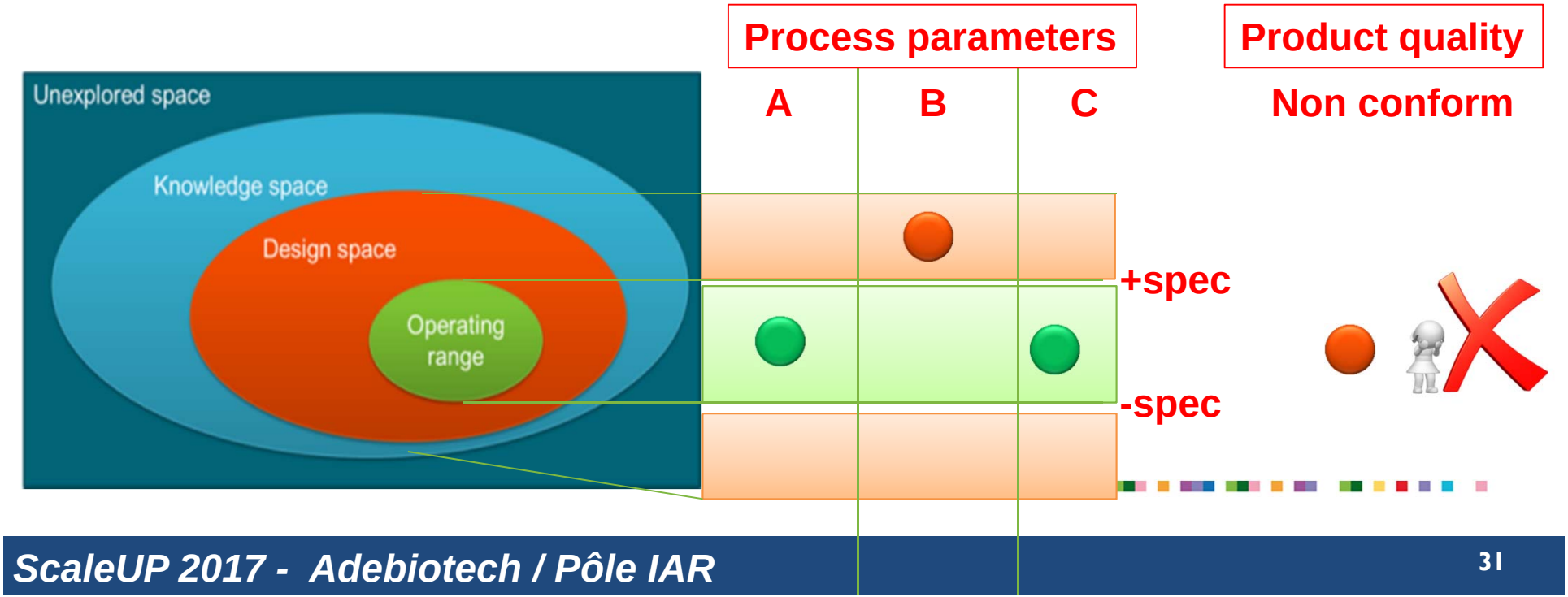


Process Analytical Technology (PAT)

FDA recommends in Q8(R2) 2009 to implement ***continuous process verification***

Manufacturing with single-use equipment

Reduces initial CAPEX, low down time, low maintenance

Product contact material should be assessed for extractible/leachable

Continuous manufacturing

Perfusion technology

Acoustic clarification

SMB chromatography

Centrifugation

Single-use industrial bioprocessing:
Cell culture and fermentation

3L Bioreactor (Merck)

Fixed-bed bioreactor (Pall)

2000L stirred (Merck)

SUB Stirred (Thermo)

Horizontal rocker (Sartorius)

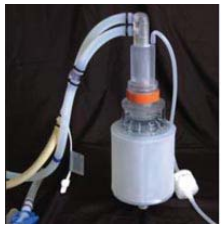
Single-use industrial bioprocessing: *Separation technology*

Filtration

Single-use TFF

Single-use NF

Single-use DF



Centrifugation

Chromatography

Single-use industrial bioprocessing
Sterile connections

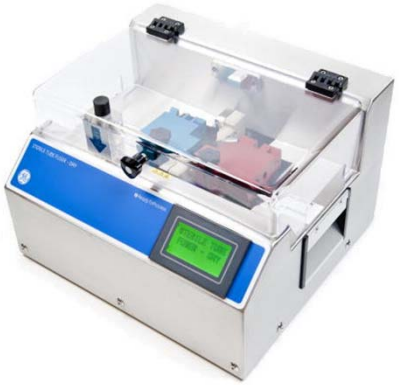
AseptiQuik S
Small format 1/8", 1/4" and 3/8" genderless connectors provide quick and easy sterile connections for low-flow applications. Learn More

AseptiQuik G
Genderless connectors enable quick and easy sterile connections, even in non-sterile environments. Learn More

AseptiQuik C
Provide quick and easy sterile connections, even in non-sterile environments. Learn More

AseptiQuik X
Large format 1" connectors provide quick and easy sterile connections for high flow applications. Learn More

Sterile (Dis)-connectors



Fuser-sealer

AseptiQuik DC
Make quick and easy sterile connections and disconnections, even in non-sterile environments. Learn More

AseptiQuik STC
Integration of AseptiQuik® sterile connector and the Steam-Thru® II Steam-in-Place connector. Learn More

Steam-Thru Connections
Quick and easy sterile connection between biopharmaceutical processing equipment and disposable bag and tube assemblies. Learn More

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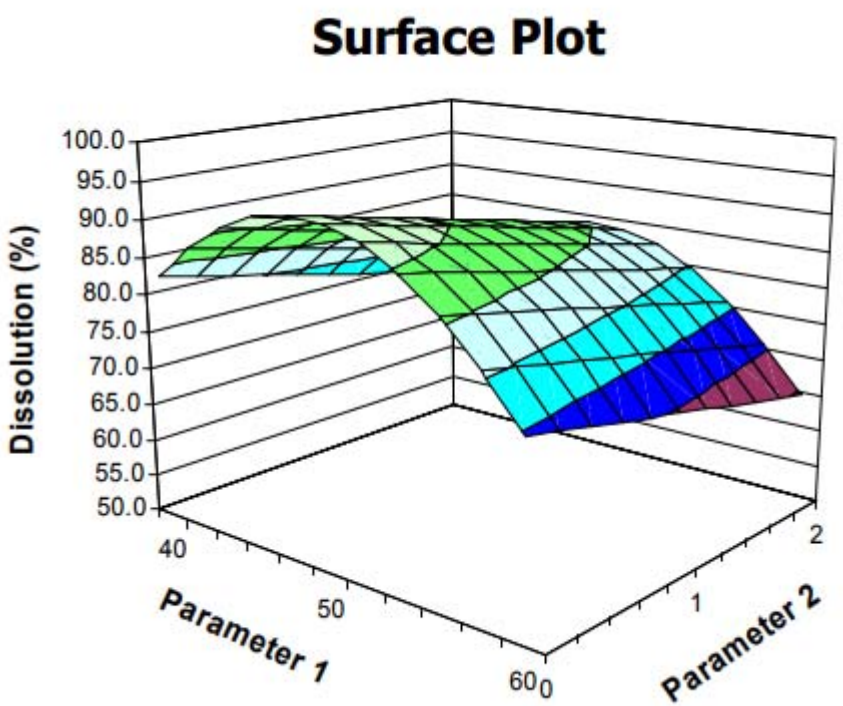
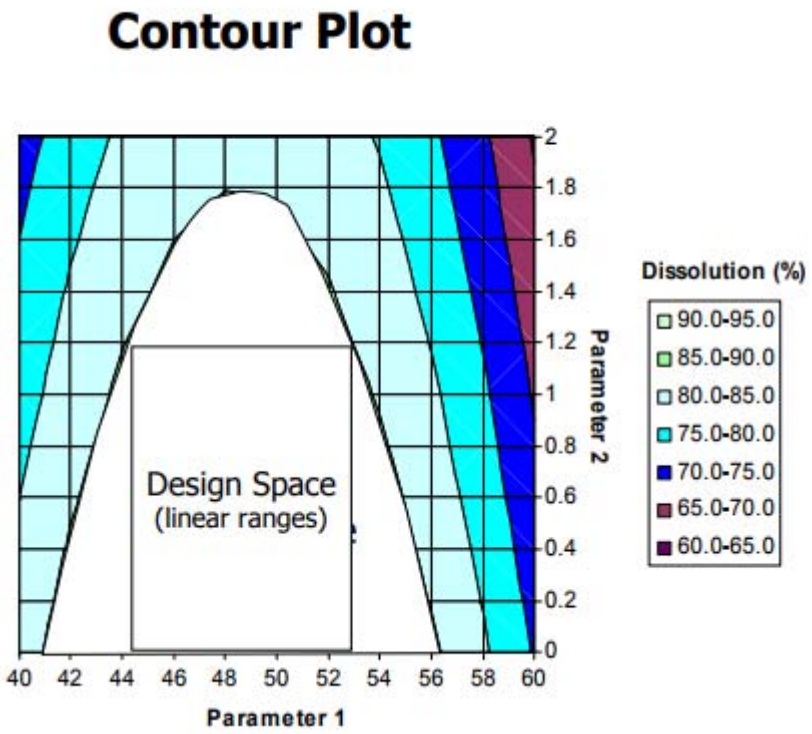
Many thanks!

Question?





- Design space can be described as a mathematical function or simple parameter range
- Operation within design space will result in a product meeting the defined quality attributes

Moheb M. Nasr, Ph.D, FDA Workshop on implementaiton of ICH Q8/Q9/Q10, 2008 .