Le « Quality by Design »

Concept et méthodologie appliquée aux produits de biotechnologie

Christian Valentin

- Les concepts Quality by Design et Process Analytical Technology
- Les textes fondateurs : ICH série Q8-Q11
- La Méthodologie QbD
- PAT et QbD en Biotechnologie

Les concepts QbD et PAT

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Origine du QbD : FDA 2002

- **Sept 2002** : FDA announced new vision for cGMPs
  - *"Pharmaceutical cGMPs for the 21st Century : a Risk-Based Approach."*
  - Goal : Modernize FDA's regulation of pharmaceutical quality

The Desired State: a mutual goal of Industry, Society, and Regulators

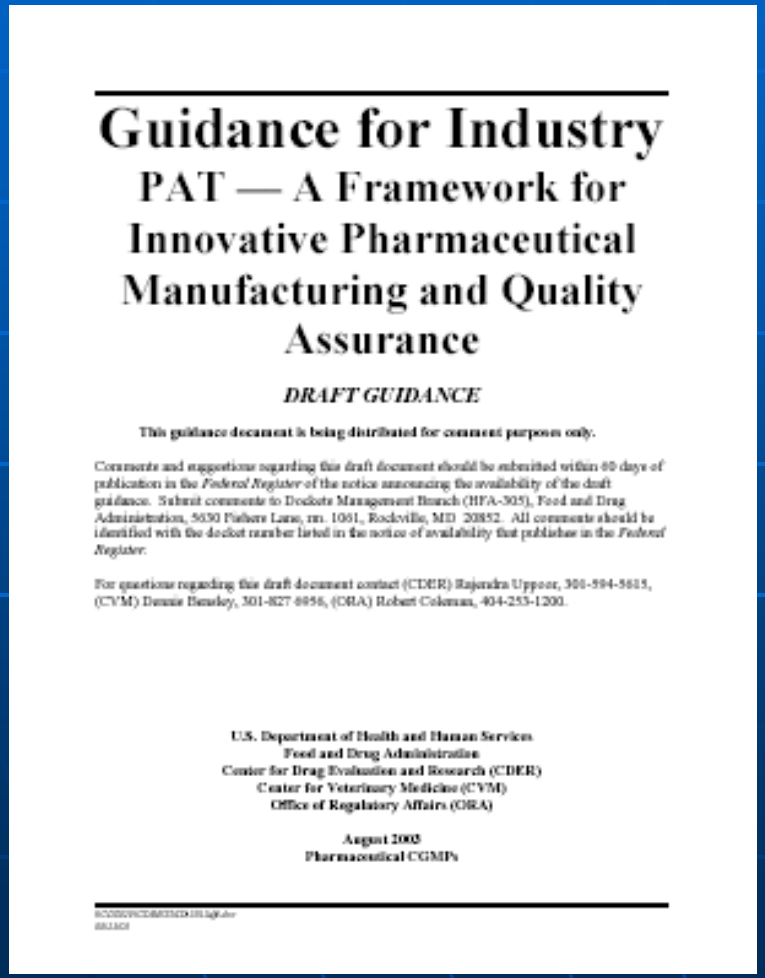
*A maximally **efficient, agile, flexible** pharmaceutical manufacturing sector that **reliably produces high-quality drug products without extensive regulatory oversight**.*

- **Sept 2004** the FDA released the PAT Guidance
  - Encourages Voluntary Development and Implementation

La phylosophie du QbD

- The product is designed to meet **patient needs** and performance requirements
  - Target product profile
- QbD is a **scientific, risk-based** approach leading to **continuous improvement**
  - The process is designed to consistently meet product critical quality attributes
- When properly implemented, **QbD improves speed to market** :
  - reduces product variation
  - Improves operating efficiency and reduces costs at all stages of the process.

PAT : Process Analytical Technology



Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

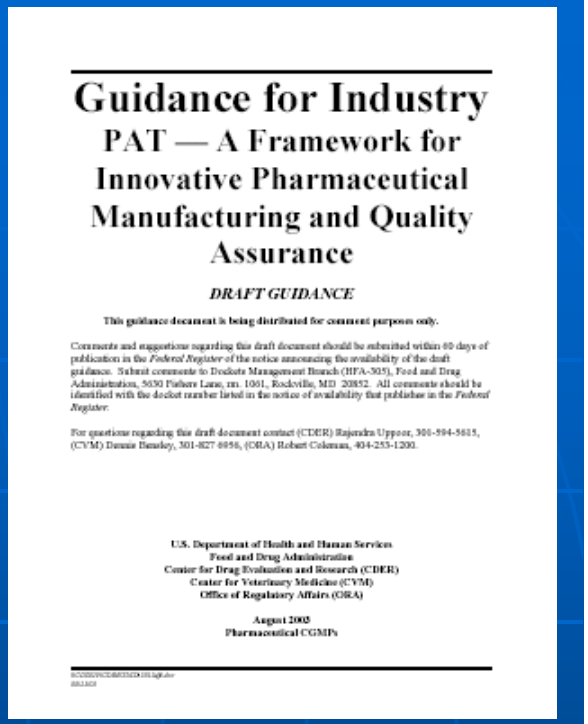
For questions regarding this draft document contact (CDER) Rajendra Uppoor, 301-594-5615, (CVM) Dennis Bensley, 301-827-6956, (ORA) Robert Coleman, 404-253-1200.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

- ✓Réduire les temps de cycle de production (et de controle)
- ✓Libération en temps réel
- ✓Bien du 1er coup (RFT)
- ✓Maitrise la variabilité
- ✓Faciliter l'amélioration continue
- ✓Accroitre l'automatisation pour réduire les erreurs humaines

- A system for …
  - = approche multidisciplinaire
- …designing , analyzing
  - = R&D / Qualité de conception
  - = gènérer et exploiter des données
- …and controlling manufacturing
  - = développement et Fabrication
  - Control = Maîtrise
- ….through the timely measurement
  - = Temps réel
- ….of Critical Quality and performance Attributes
  - = Produit
- …of raw and in-process material and processes
  - = Composants et Paramètres Critiques du Procédé
- …with the goal of ensuring final product quality



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August 2003
Pharmaceutical CGMPs

Un peu de réglementaire

- Les concepts Quality by Design et Process Analytical Technology
-
- Les textes fondateurs :
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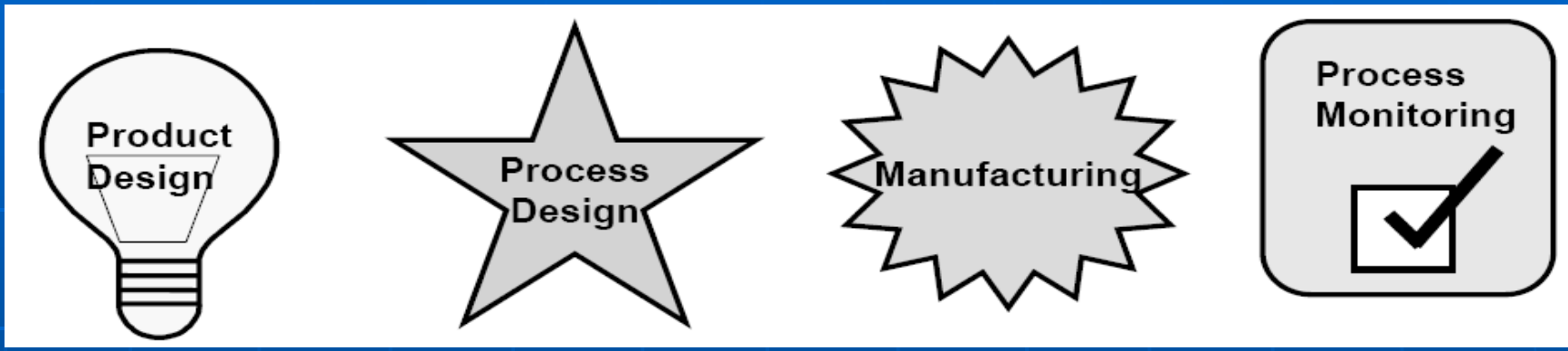
La trilogie ICH : Q8-Q9-Q10



ICH Q8(R2) "Pharmaceutical Development" (concept paper 2005 – revu en 2009)

ICH Q11: Development and manufacture of drug substances (2012)

PAT Guidance (2004)

ICH Q9 "Quality Risk Management" (2005)

ICH Q10 "Pharmaceutical Quality Systems (2008)

ICH Q8 : développement pharmaceutique

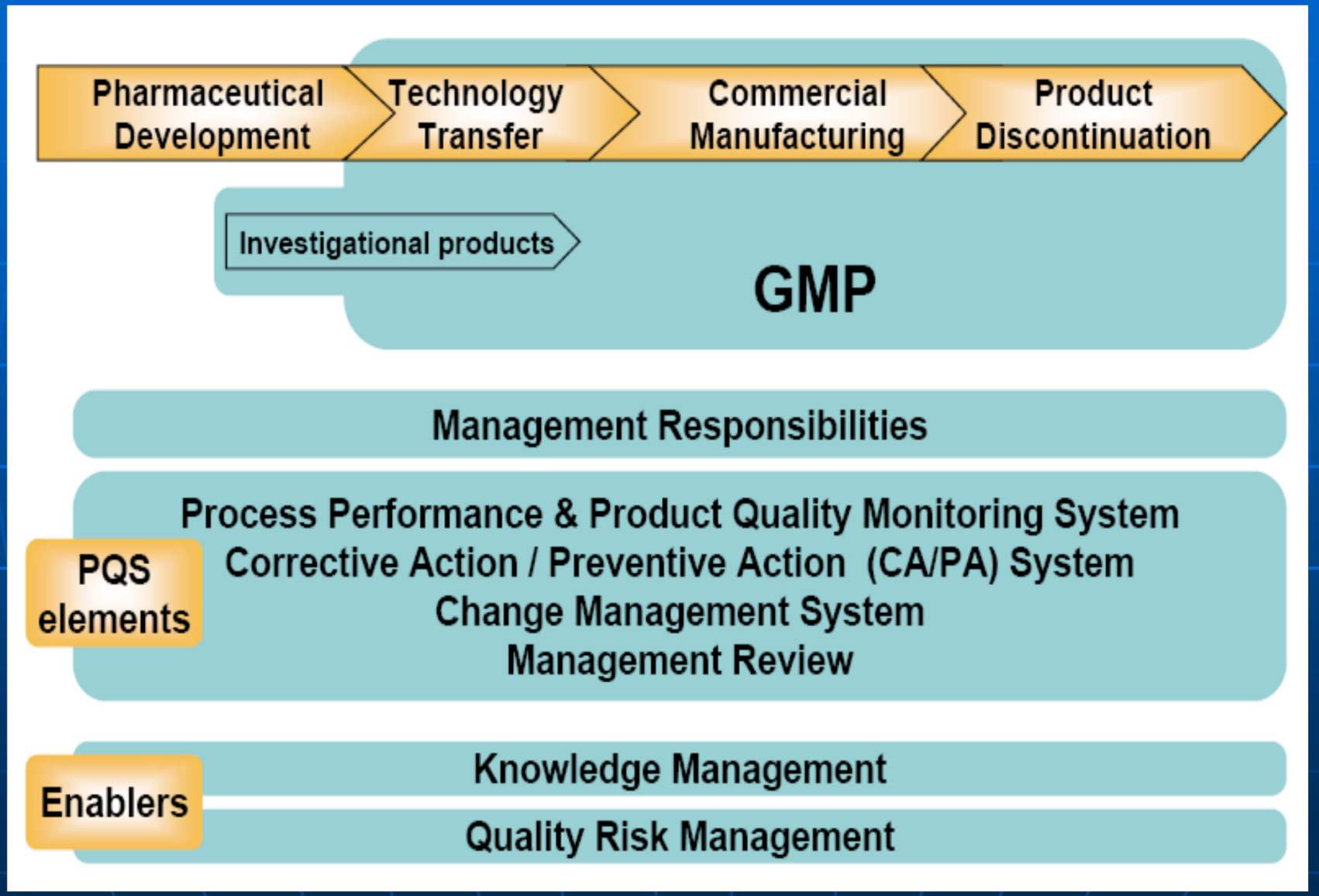
Aspects	Current	Quality by Design
Pharmaceutical Development	**Empirical,** univariate	**Systematic, Mulitivariate**
Manufacture process	**Fixed** Validation of **3** full scale **batches** focus on **reproducibility**	**Adjustable** within Design space, **continuous verification** within **design space**, focus on **robustness**
Process control	In-process testing for go/no-go **off line** analysis **slow response**	**PAT** utilized for feed back and **feed forward at real time**
Product specification	Quality control, **batch data**	based on desired **product performance**
Control strategy	Mainly by intermediate and **end product testing**	Risk based controls shifted upstream, **real time release**
Lifecycle management	**Reactive** to problems & OOS; **Post-approval changes** needed	**Continual improvement** enabled within design space

ICH Q9 :gestion du risque qualité

- Méthodologie d'analyse de risque :
  - Cartographie du procédé :
    - Étapes , paramètres critiques
  - Analyse et quantification du risque
    - Action
    - ré-évaluation du risque

- Les Outils d'analyse de risques
  - Ishikawa
  - méthode 5M
  - AMDEC
  - .../...

ICH Q10 : système qualité



PQS=Pharmaceutical quality system

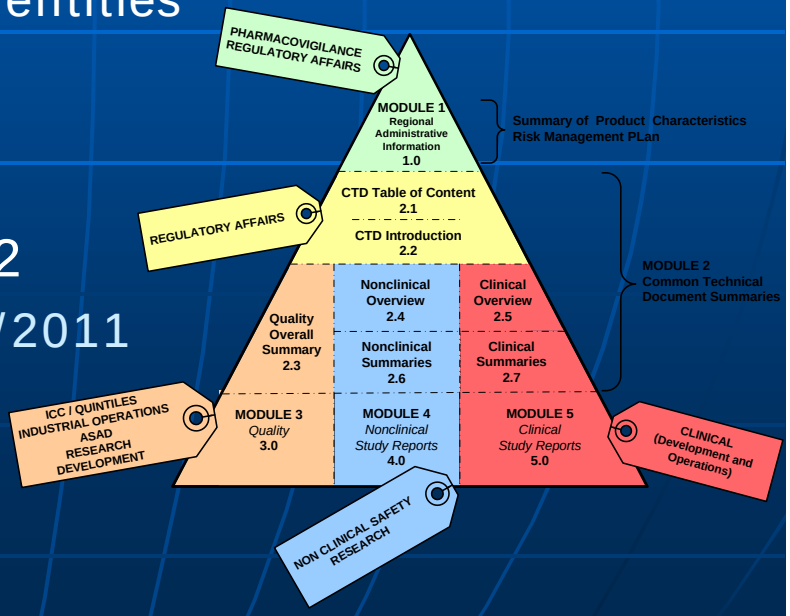
Evolution des standards qualité:

- Current GMP:
  - Quality by Control
  - Specifications
  - Validation
  - Change control
  - Batch release
- 21st Century GMP:
  - Quality by Design
  - Process understanding
  - Design space
  - Continuous improvement
  - Real time product release

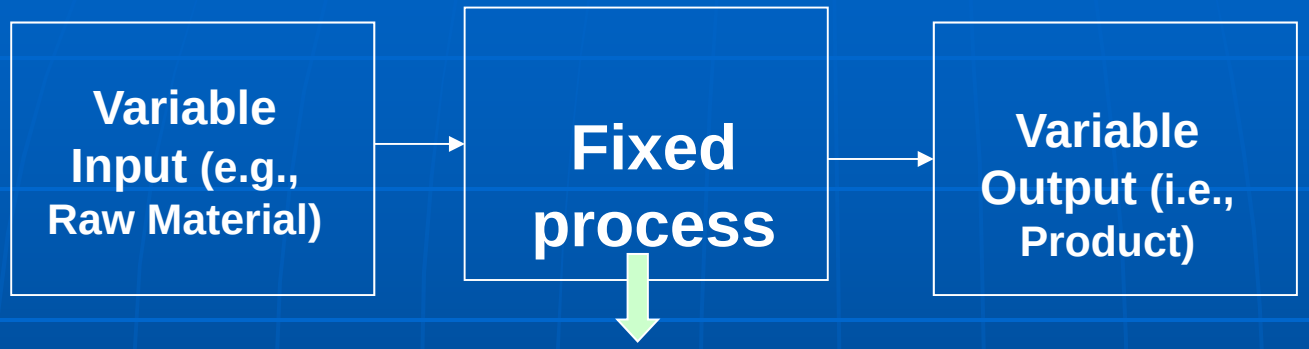
ICH Q11: Development and manufacture of drug substances

- *Step 4* of the ICH process on May 2012.
  - This new guidance is proposed for Active Pharmaceutical Ingredients **(APIs)** harmonising the scientific and technical principles relating to the description and justification of the development and manufacturing process (CTD sections S 2.2. - S 2.6)_of Drug Substances_**including both chemical entities and biotechnological/biological** entities

- *Step 5*
  - *EU:* Adopted by CHMP, May 2012
    - issued EMA/CHMP/ICH/425213/2011
  - *MHLW and FDA:*
    - To be notified



En résumé : du QbC au QbD



QbC

Current state

cGMP

QbD

Desired state

Design Space

* As appropriate based on process understanding

Méthodologie QbD et PAT

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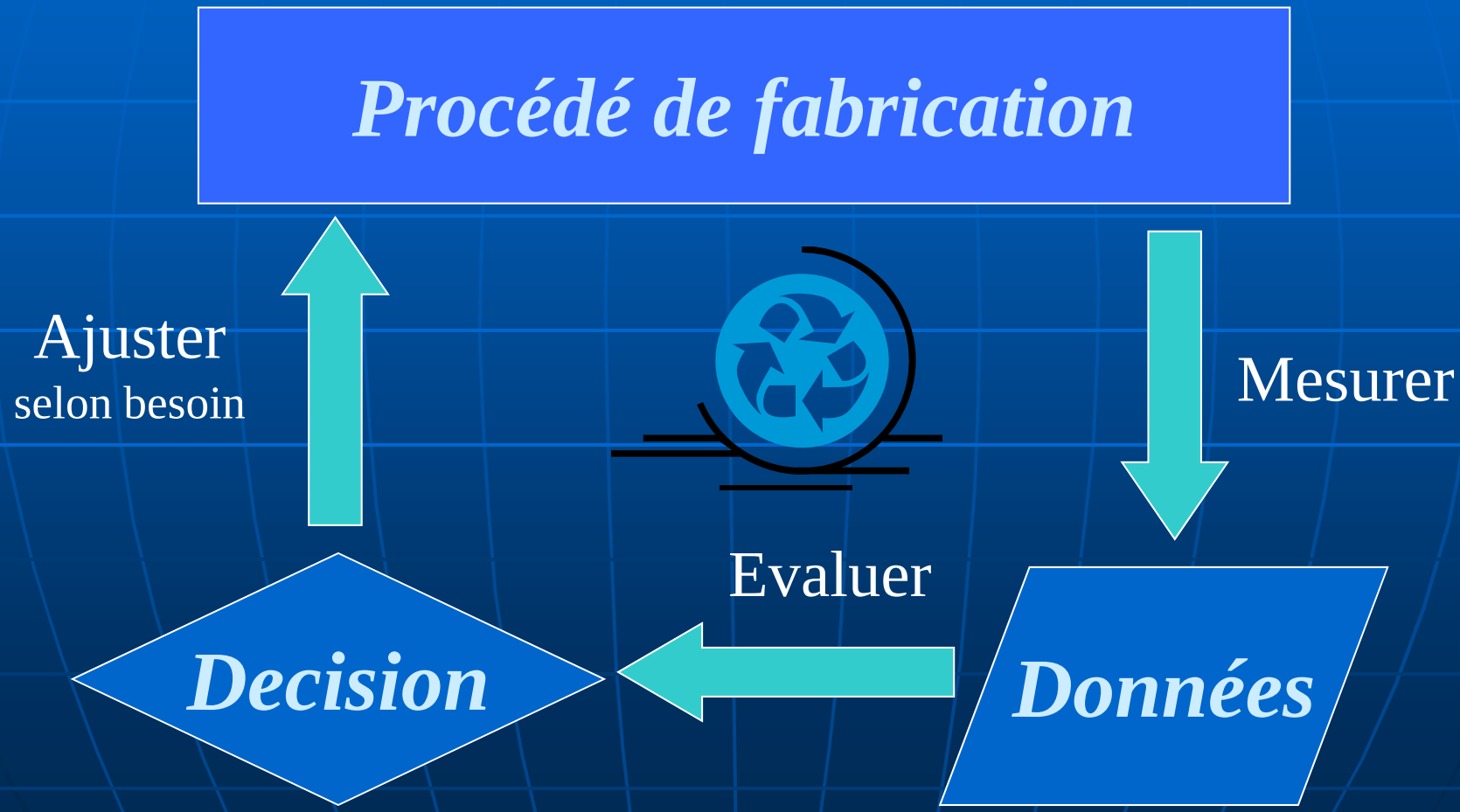
Quality by Design (QbD)

- **Definition selon ICHQ8 (R2)**
  - “A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management“
  - Les principales étapes d’une approche Quality by Design

PAT : Process Analytical Technology : un processus d'amélioration continue



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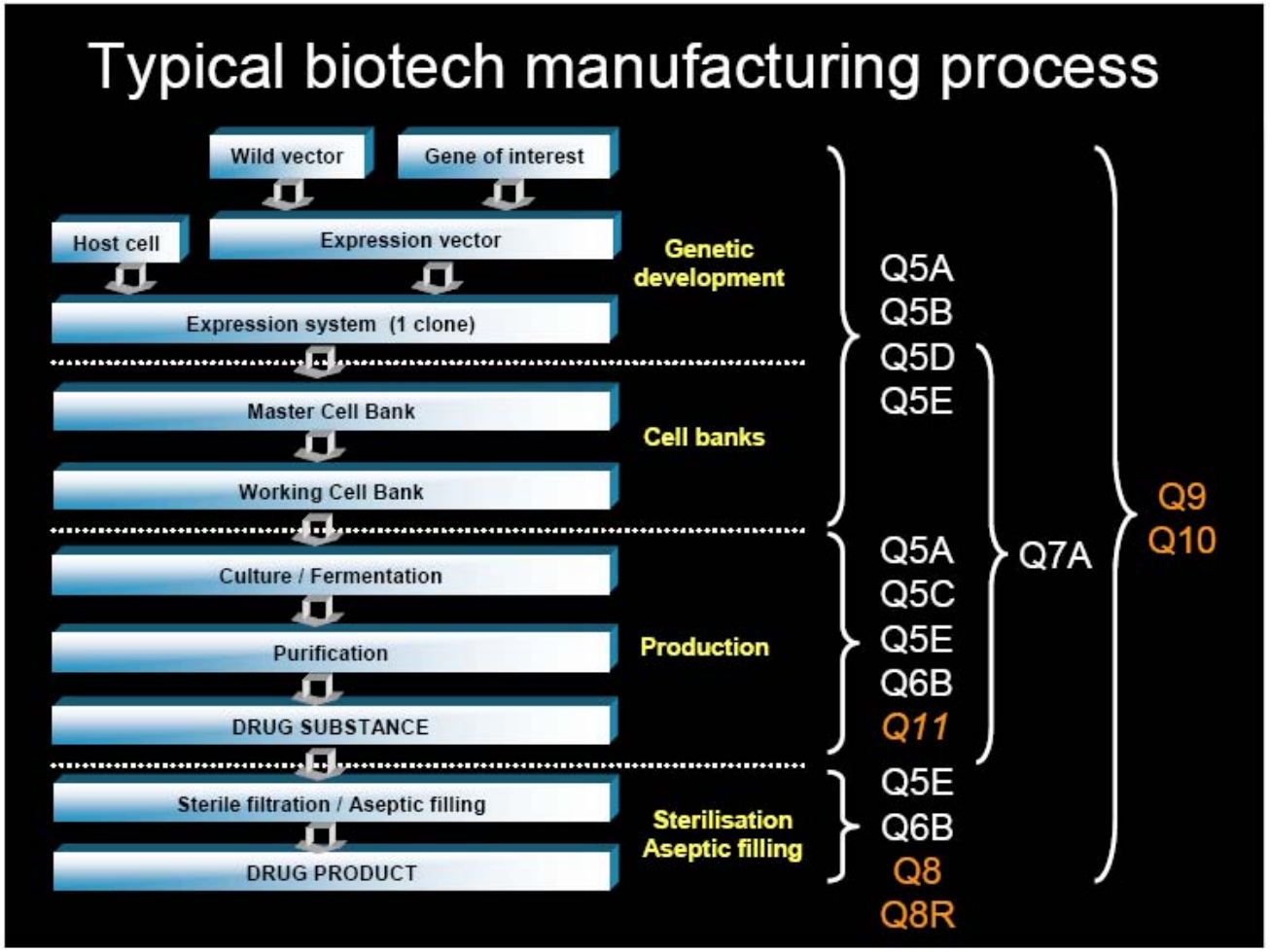
ICH 1990' : « Q5 » Serie

Genetic engineering :



Conventional drug

- Made by **mixing chemicals**
- Mostly **small**, relatively **simple** molecules
- can usually be shaped into a pill oral administration
- Around **50 monitoring** and quality tests for a traditional (chemical) medicine
- Conventional drugs, based on relatively simple molecules,
- **Easy to copy : generics**

Biotech / Biologic

- **Far more complex**, mimicking **large substances** produced by the human body (enzymes, insulin, antibodies…)
- Biotech drugs are grown **in live cells** in a **bioreactor** and then **purified**.
- for injection administration
- **Complex molecules** : high level of monitoring and quality testing (around **250 in-process tests** are conducted for a biological medicine)
- Unique **starting material** and complex manufacturing processes make it more difficult to exactly reproduce /copy : **Biosimilars**

QbD et biomolécules

- **Mabs : a common technology Plateform to deliver several products**
  - Higher knowledge based : CHO , DSP and formulation
  - Quicker RoI : One common process to deliver several products

- **Recombinant therapeutics proteins :**
  - Diversity of expression systems : eucaryote , bacterial , yeast ...
  - DSP and formulation process specific issues

- **Vaccines :**
  - Higher level of Complexity : Huge diversity of Antigens
  - several technologies needed to get one product
  - Multicomponent drug product : Combination and Adjuvantation

CMC Biotech Working Group

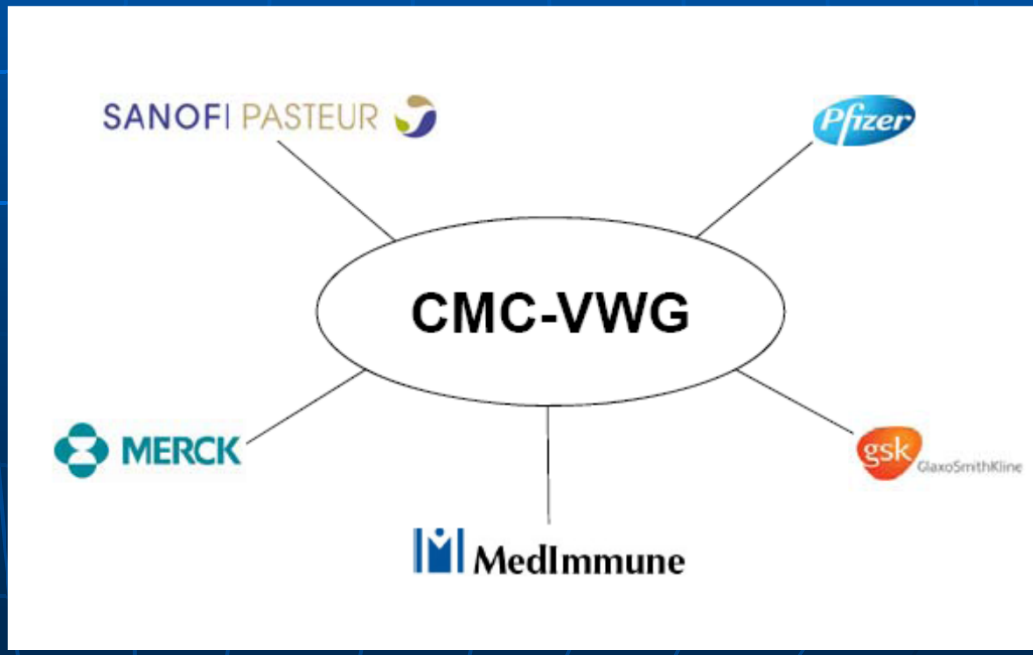
Pfizer · MedImmune · Genentech (A Member of the Roche Group) · Lilly · Abbott · GlaxoSmithKline · Amgen

A Mab case study

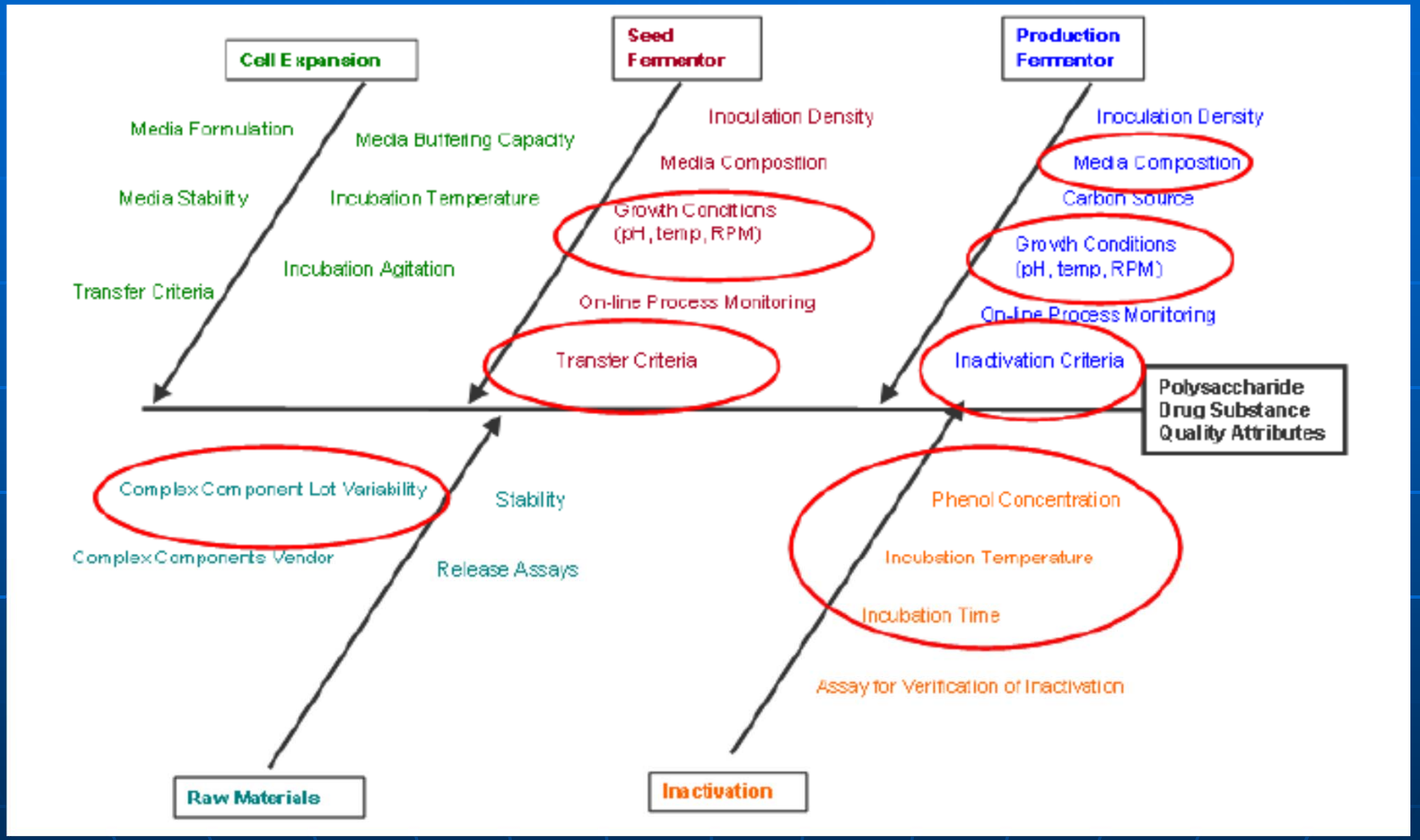
2009-2011

A VAX case study

2011-2012

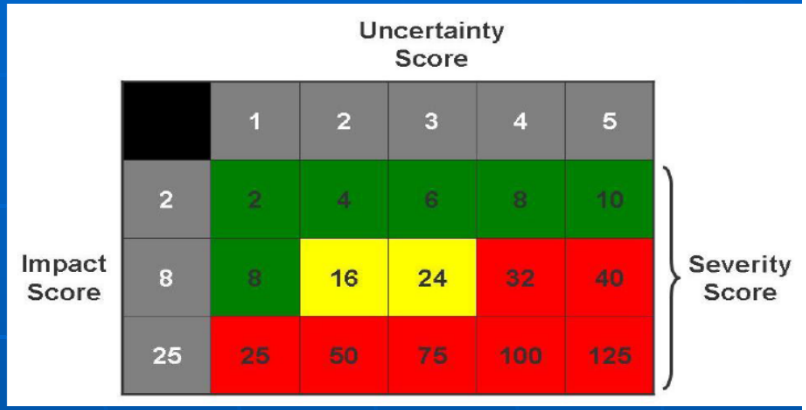


Mapping d'un procédé : upstream (A Vax)



outil d'analyse de risque

Quantification d'un risque :
Severité = Fréquence × gravité
(x Detectabilité)



- **CQA acceptance criteria generated from existing data / prior knowledge from :**
  - ✓ non-clinical data
  - ✓ clinical data
  - ✓ literature
  - ✓ experience with similar products

Relation entre CQAs et CPP
(A Mab : purification)

Table 4.2 Quality Attributes Potentially Affected by the A-Mab Downstream Unit Operations

Quality Attributes	Risk of Impact to Product Quality Attribute						
	Protein A Chromatography	Low pH Treatment	Cation Exchange Chromatography	Anion Exchange Chromatography	Small Virus Retentive Filtration	Ultrafiltration and Diafiltration	Final Filtration and Bottling
Identity							
Protein Content						✓	
ADCC							
Aggregate	✓	✓	✓	✓	✓	✓	
Color							
Clarity							
Oligosaccharide Profile							
Charge Variants	✓	✓	✓	✓			
pH						✓	
Osmolality						✓	
Residual HCP	✓	✓	✓	✓			
Residual Protein A	✓	✓	✓	✓			
Residual DNA	✓	✓	✓	✓			
Residual Methotrexate	✓		✓	✓		✓	
Bioburden							✓
Endotoxin			✓	✓			
Viral Safety		✓		✓	✓		

Gestion de la connaissance et maitrise du risque (A vax)

Initial CQAs

Attribute	S
Potency : types 1-4	50
Potency: type 5	16
Potency: Animals	50
Peptidoglycan Level	24
VLP Fragments (Assembly)	32
Residual DNA	75
Extent-of-Conjugation	75
Completeness-of-Adsorption	125
Appearance	2
Osmolality	32

→

Post P2 CQAs

Attribute	S
Potency : types 1-4	50
Potency: type 5	16
Potency: Animals	50
Peptidoglycan Level	16
VLP Fragments (Assembly)	32
Residual DNA	75
Extent-of-Conjugation	75
Completeness-of-Adsorption	75
Appearance	2
Osmolality	24

→

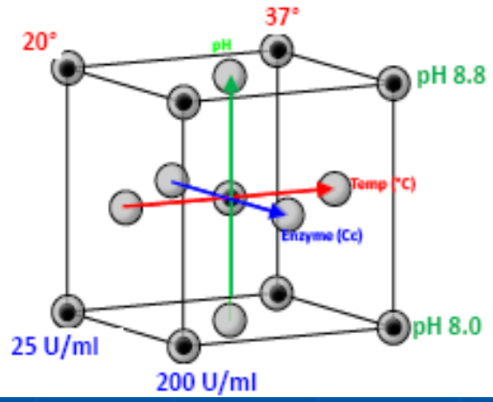
Licensure CQAs

Attribute	S
Potency : types 1-4	50
Potency: type 5	16
Potency: Animals	50
Peptidoglycan Level	8
VLP Fragments (Assembly)	24
Residual DNA	75
Extent-of-Conjugation	75
Completeness-of-Adsorption	16
Appearance	2
Osmolality	8

Définir le design space : DoE

Factor	High	Middle	Low
Temperature	37	28.5	20
pH	8.8	8.4	8.0
Enzyme cc	200	112.5	25

Fixed parameters
- incubation time
- enzyme batch
- mixing conditions

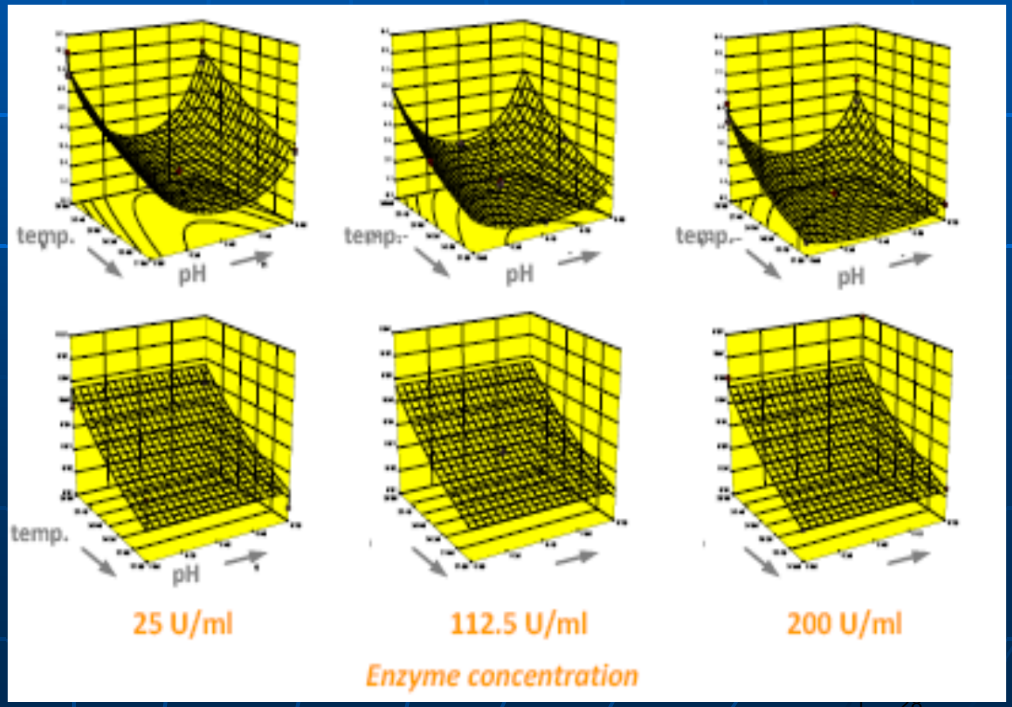


DoE PS extraction :
Enzymatic processing
For PS extraction

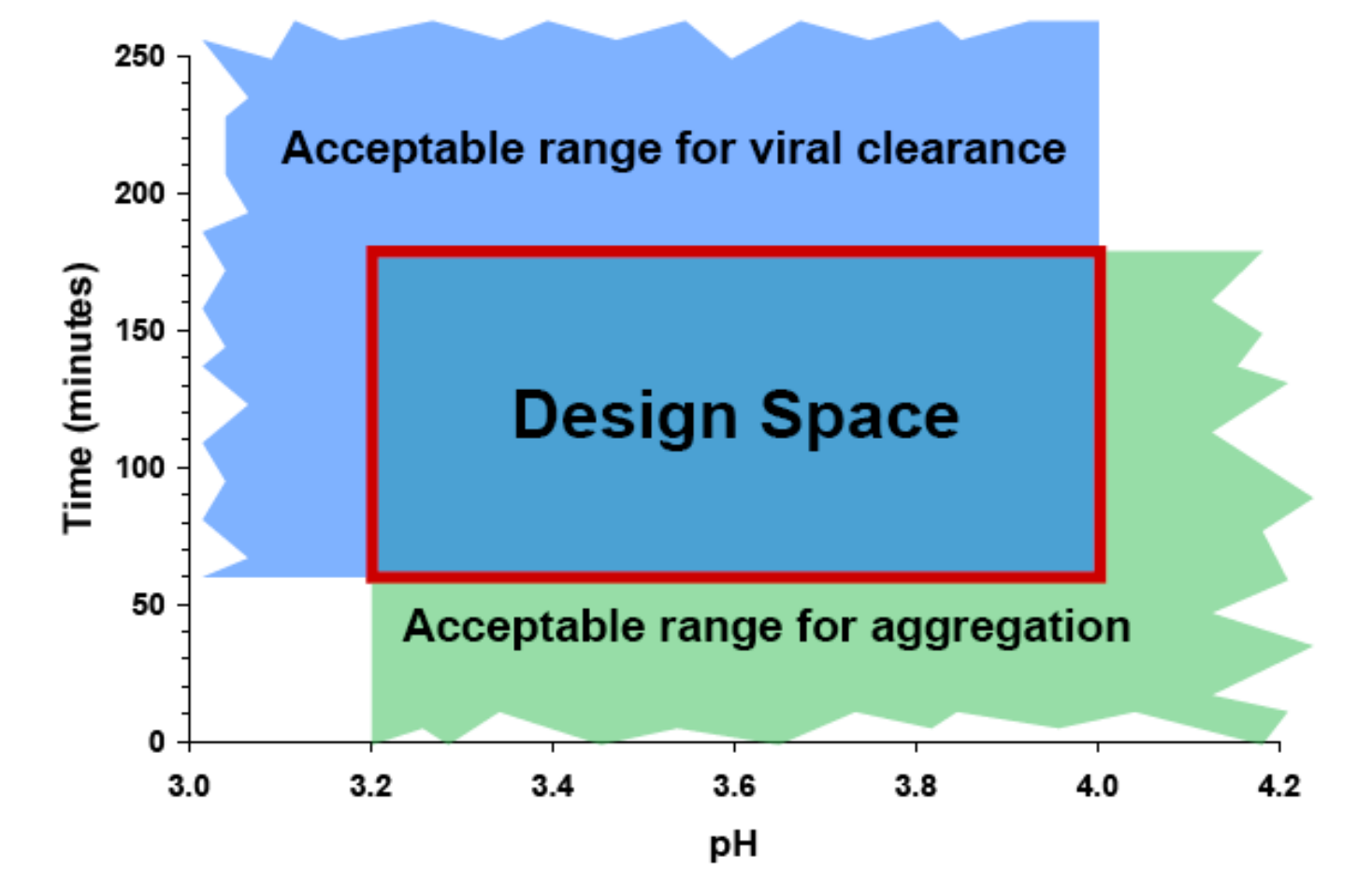
(A vax)

DoE Impurity removal :
Residual PG content as function of pH and T° at 3 enzyme concentration

(A Vax)

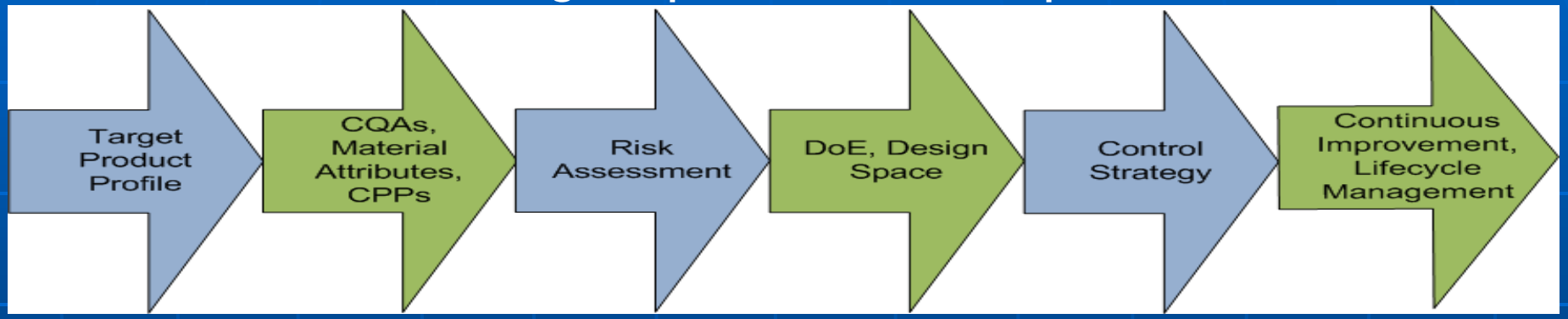


Un exemple de **design space** (A Mab)



Pour conclure … à retenir

- **QbD et PAT** : un concept encore récent (2004) - une méthodologie qui se met en place …



- **… « Parler le QbD »**
  - Produit : QTPP et CQA
  - Procédé : PP et CPP
  - QbD : renforcer sciences , qualité
  - Outils QbD et PAT : management du risque , DoE , process monitoring (capteurs en ligne), gestion et analyse de données (PLS , MVA …)
  - Contrôle : RTR
  - Design space (soumis et **approuvé** par autorités)

Opportunités et enjeux du Quality by Design :

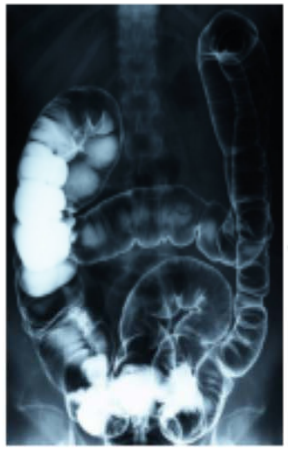
- Conception d'un produit centré sur les **besoins du patient** :
  - Focus sur les attributs qualité du produit
  - Efficacité+innocuité = f(Qualité)

- Renforcement de la **connaissance procédé** :
  - Identification et maitrise des paramètres critiques du procédé qui garantissent la maitrise des attributs Qualité du produit

- Amélioration en **Qualité** et Gain en **productivité** :
  - Qualité : réduction des phases « en aveugle » , à risque
  - productivité : PAT et potentiellement Real time release (temps de cycle)

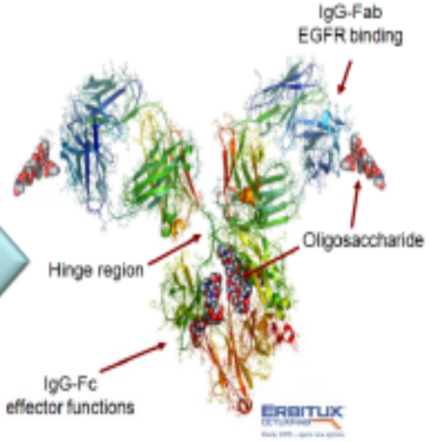
- **Amélioration continue** (life cycle management):
  - Amélioration du procédé … une fois le **Design Space** approuvé par l'autorité (flexibilité réglementaire)

Patient / produit / procédé



Clinical safety and efficacy

Link



CQAs:
Attributes by design
Variants
Impurities

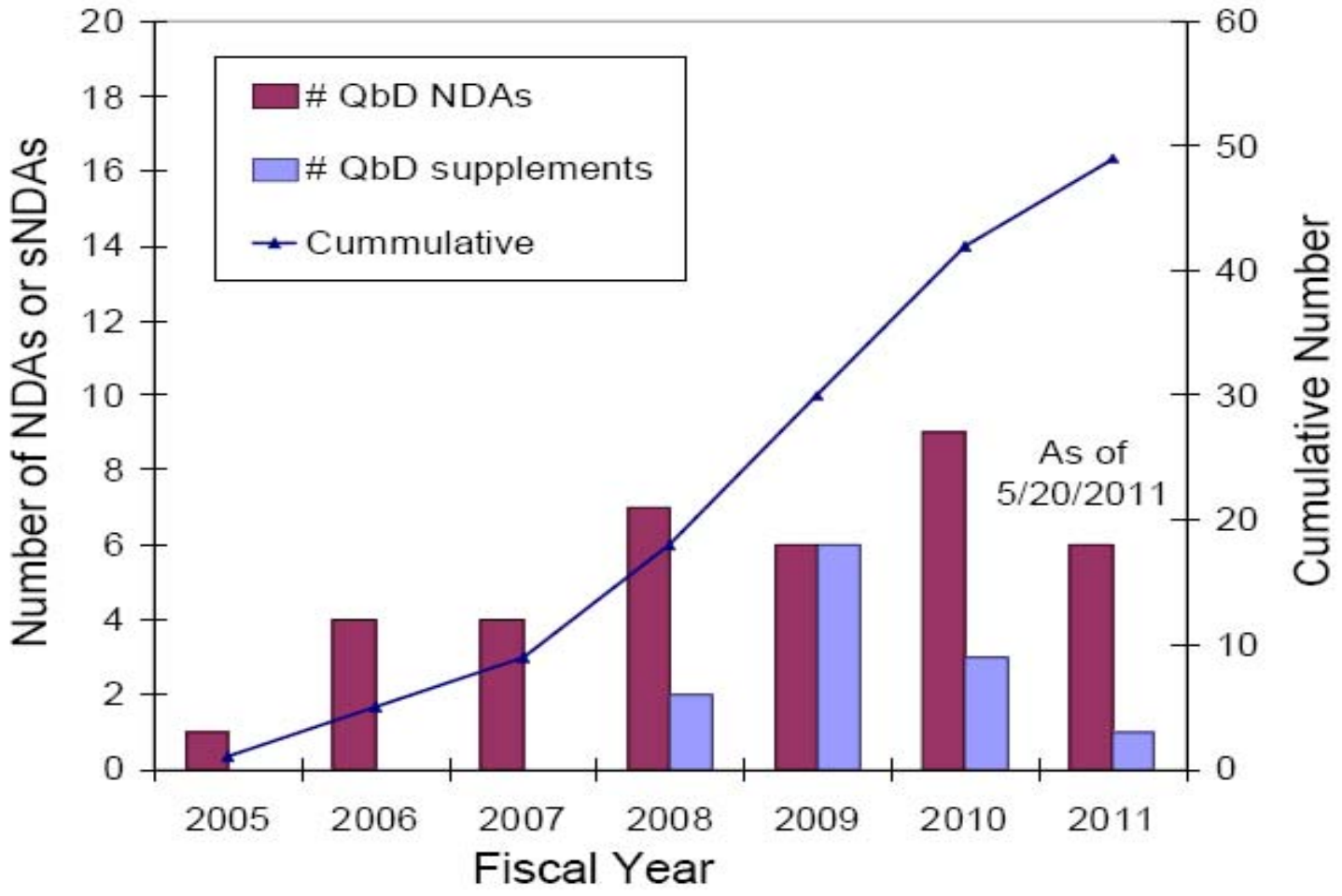
Link

CPPs:
Process parameters
Raw materials

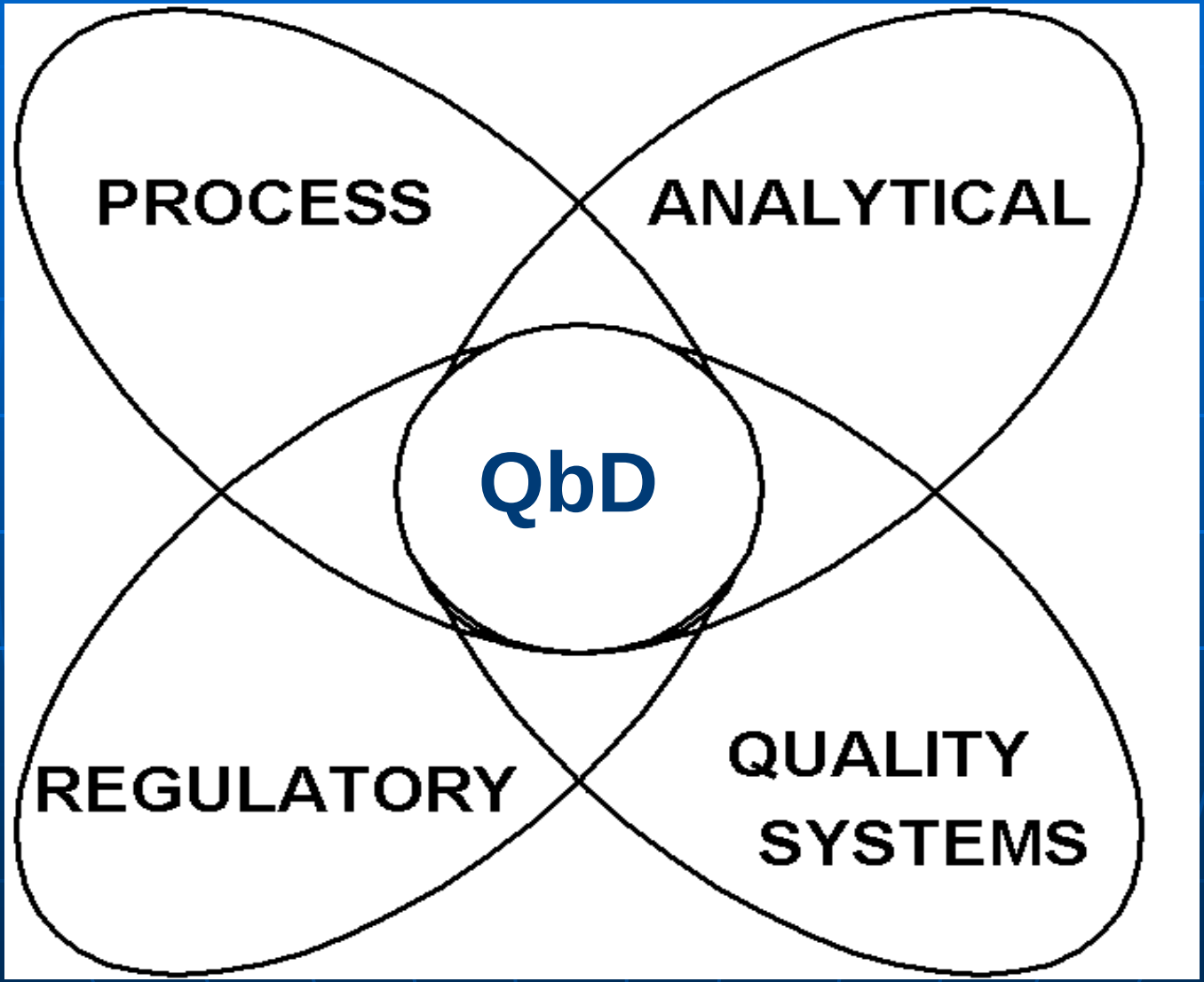
Hervé Broly - Merck Serono , congrès SFSTP Juin 2012

U.S. Food and Drug Administration
Protecting and Promoting Public Health

New Drug QbD Submissions



QbD et PAT : un travail d'équipe



Qlq références

- PAT guidance for industry
  - www.**fda**.gov/downloads/.../**Guidance**s/ucm070305.p
- A Mab case study
  - www.ispe.org/pqli/a-**mab-case-study**-version-2.1
- A Vax case study
  - www.pda.org/Home-Page-Content/CMC-VWG-A-**VAX**.aspx

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