3ª Giornata di Studio
L'applicazione del Quality by Design (QbD) nella produzione dei medicinali

Università degli Studi di Milano
27 Aprile 2015

QbD nella formulazione e nella produzione: esempi di farmaci proteici

Marta Galgano, Marco Adami, Antonella Lanati,
Franco Pattarino, Paola Scolari, Bice Conti, Maria Cristina Bonferoni

Gruppo di Lavoro Medicinali Biologici e Terapie Avanzate AFI

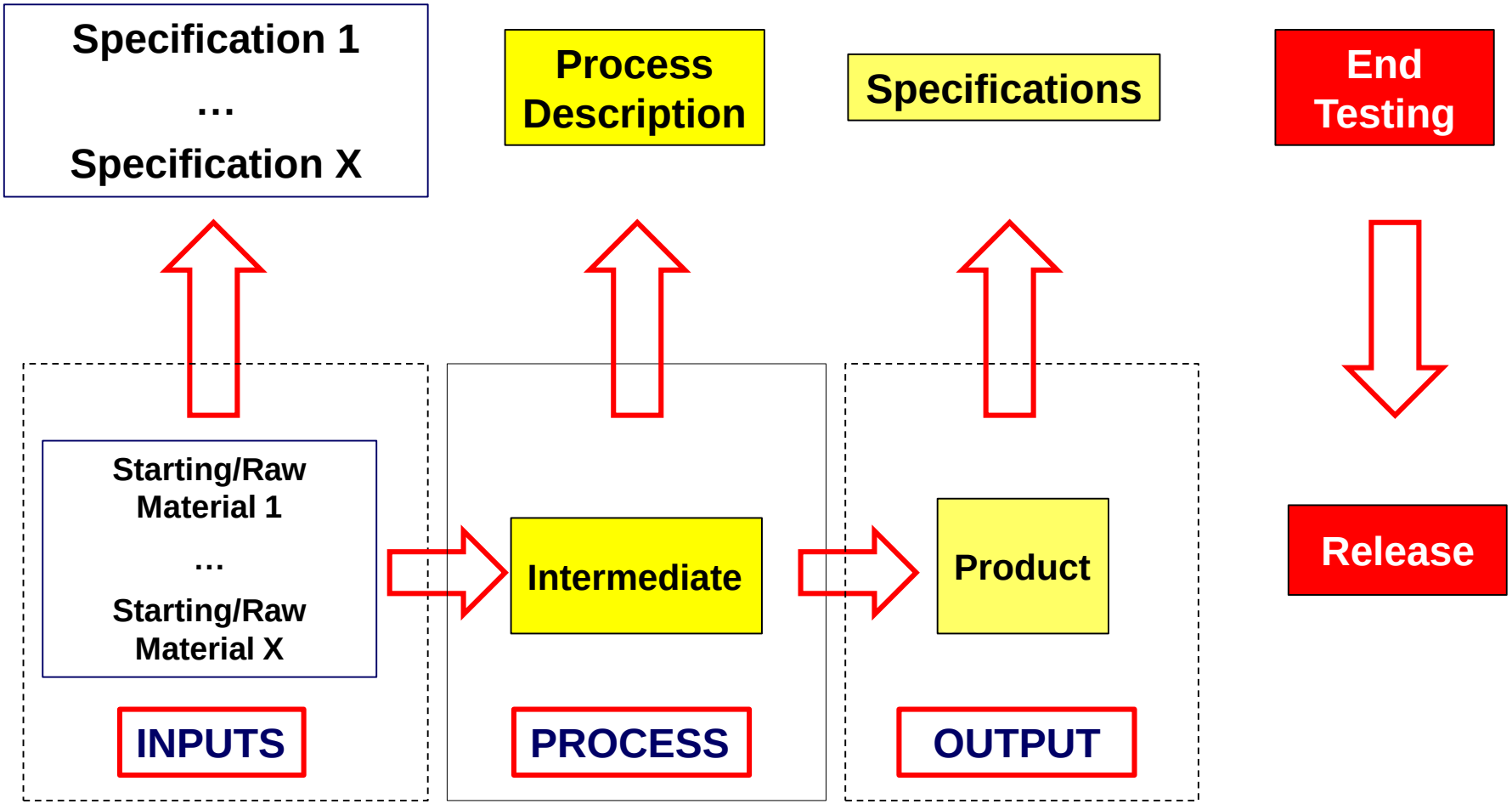
Quality by Design

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

(ICH Q8)

- Product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches
- The impact of starting raw materials and process parameters on product quality is well understood
- Emphasizes product and process understanding and process control
- The process is continually monitored, evaluated and updated to allow for consistent quality throughout product life cycle

Traditional Approach



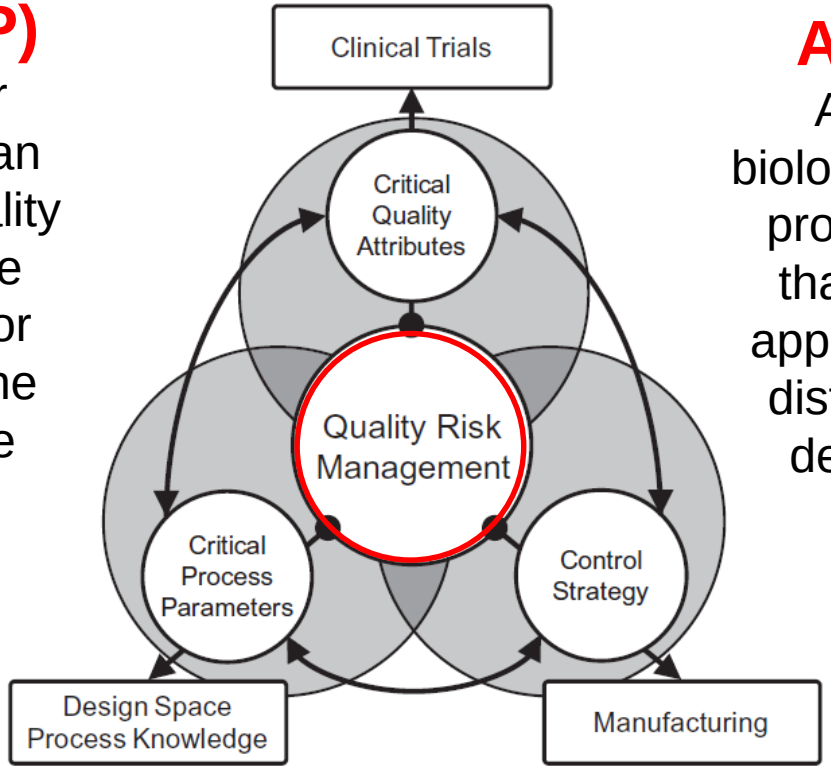
QbD Approach

Quality Target Product Profile (QTPP)

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product

Critical Process Parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality



Critical Quality Attribute (CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

Rouiller Y. et al., EJPB 2012

- **ICH Q8:** Pharmaceutical Development should include, ***at a minimum***, the following elements:
  - ✓ Quality Target Product Profile (QTPP)
  - ✓ Identification of potential critical quality attributes (CQAs) of the Drug Product, so that those product characteristics having an impact on product quality can be studied and controlled
  - ✓ Determine the critical material attributes (CMAs) of the Drug Substance, excipients, etc., and selection of the type and amount of excipients to deliver drug product of desired quality
  - ✓ Selection of an appropriate manufacturing process
  - ✓ Definition of a control strategy
    - A planned set of controls (related to Drug Substance and Drug Product materials and components, facility and equipment operating conditions, IPCs, and finished product specifications) derived from current product and process understanding that ensures process performance and product quality

BIOLOGICALS

Drug Substance

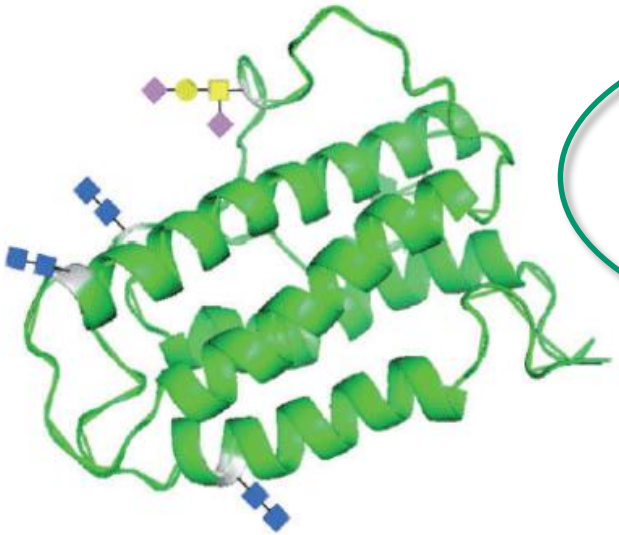
Drug Product

ICH Q11

The considerations for design space addressed in ICH Q8 for an enhanced approach to the development of the drug product are applicable to drug substance.

In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.

BIOLOGICALS



Complexity of structure

Complexity of manufacturing process

The identification of CQAs for complex products can be challenging. Biotechnological/biological products, for example, typically possess such a large number of quality attributes that it might not be possible to fully evaluate the impact on safety and efficacy of each one.

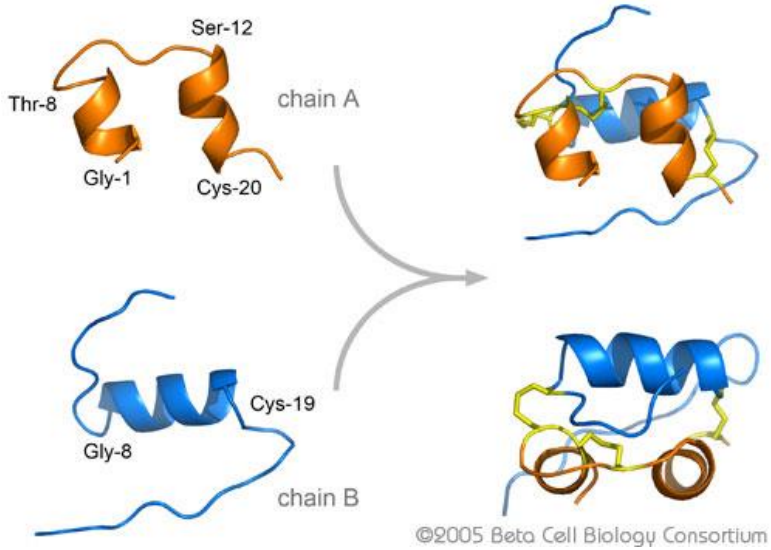
ICH Q11

Key role of RISK ASSESSMENT

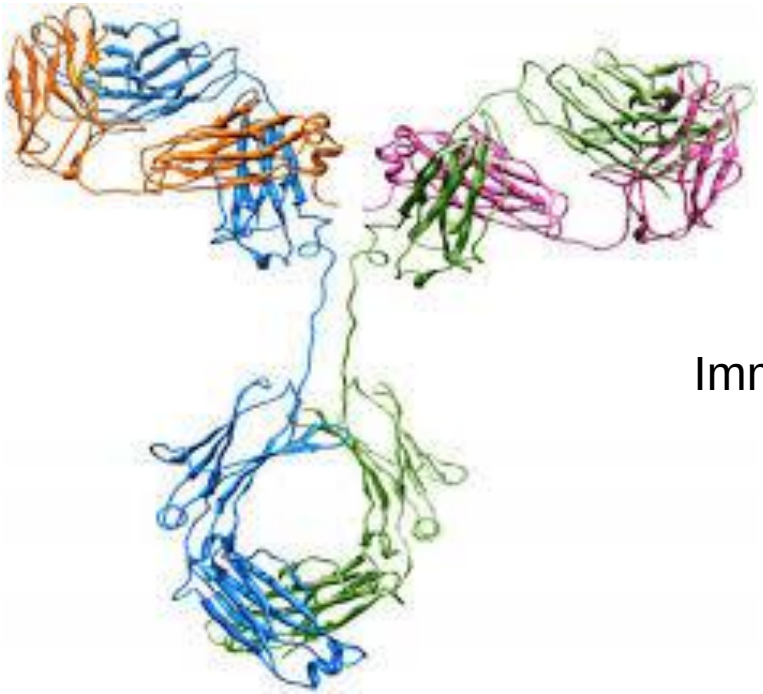
Complexity of structure

Therapeutic proteins

Insulin

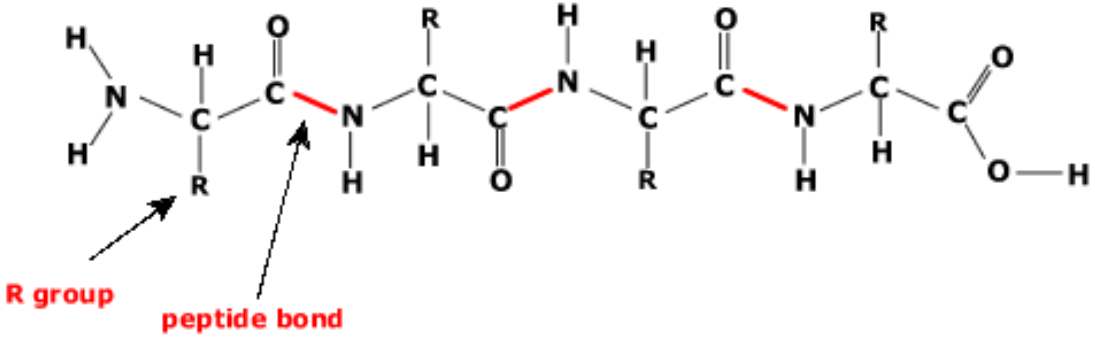


Monoclonal antibodies



Immunoglobulin G

PROTEIN INSTABILITY



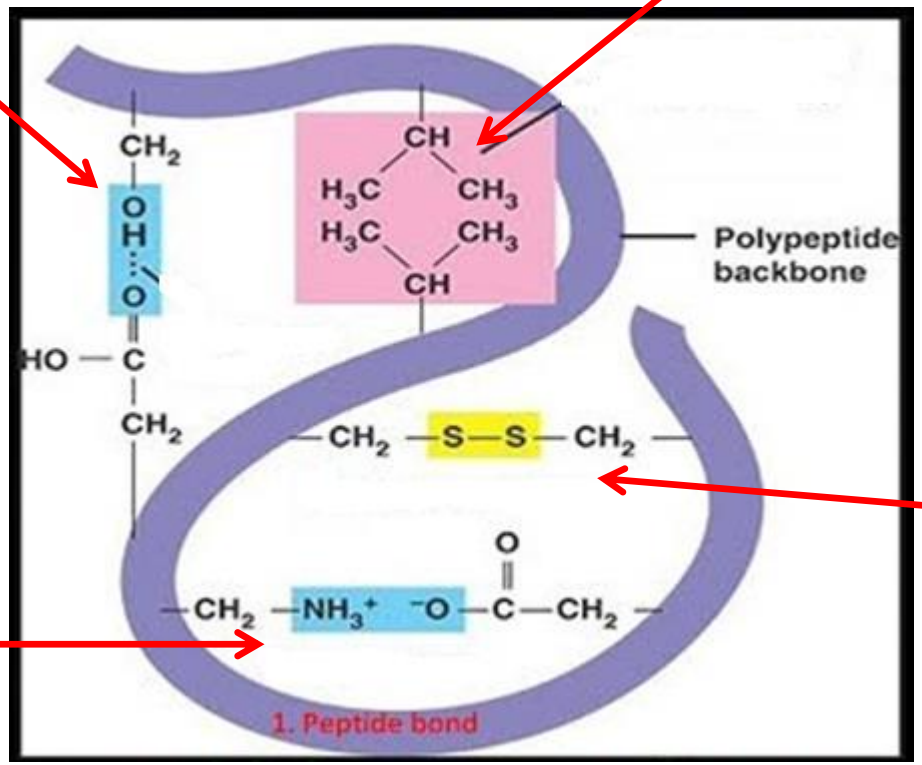
Deamidation (Asn, Gln) Hydrolysis	pH
Oxidation (Cys, Met, His, Trp, Tyr) Isomerization	Oxidants, metal ions, light, pH

PROTEIN INSTABILITY

Hydrophobic interactions:
(usually inside the protein structure)

Hydrogen bonds:

Non-aqueous solvents (ethanol, acetone)



Temperature
Surfactants
Shear
Foam

Disulfide bonds:

Disulfide bond breakage and exchange

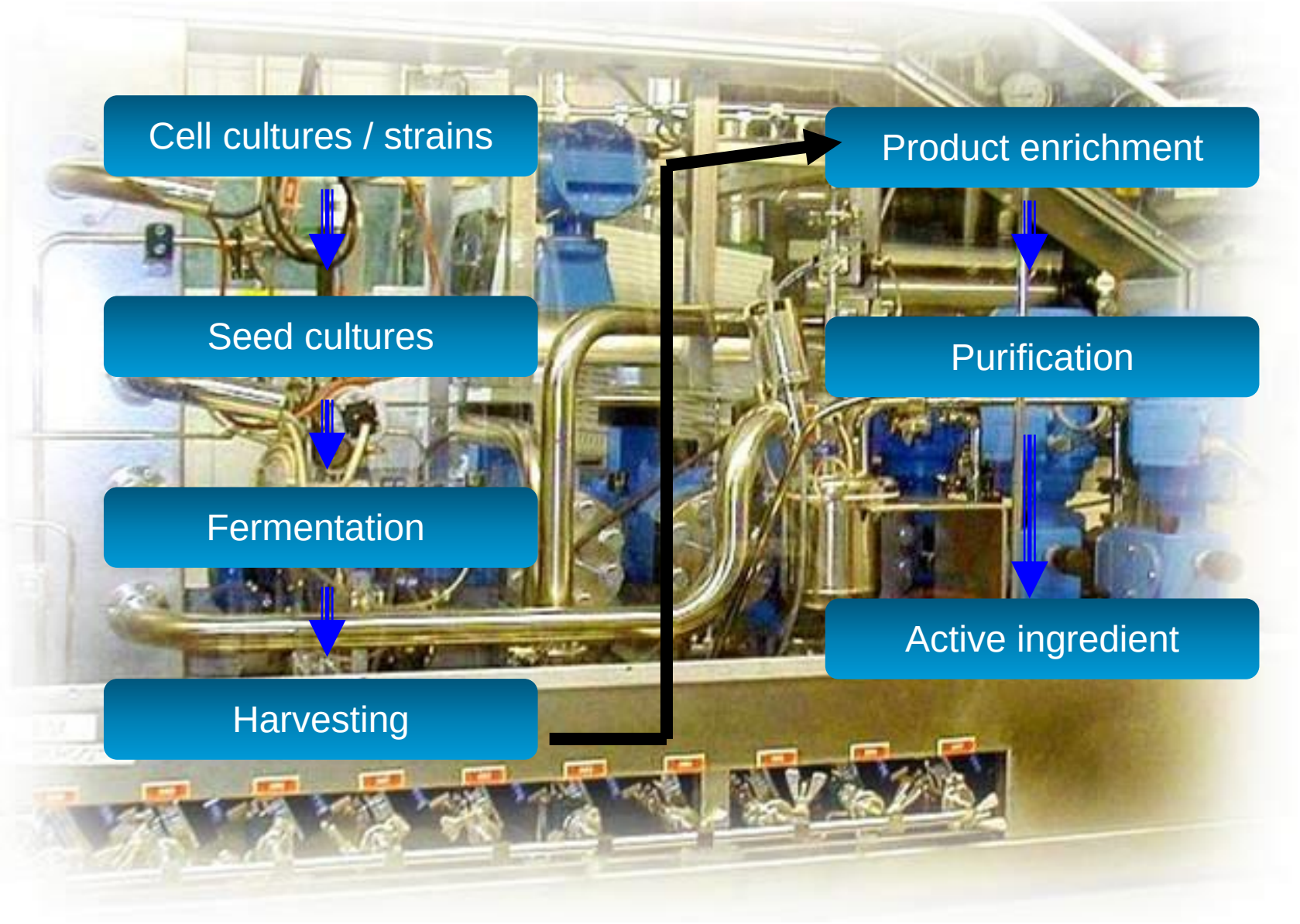
Ionic bonds:
(asp or glut acid, lys, arg)

pH, organic solvents

Aggregation, Folding, Unfolding

Solubility, activity, immunogenicity

MANUFACTURING PROCESS

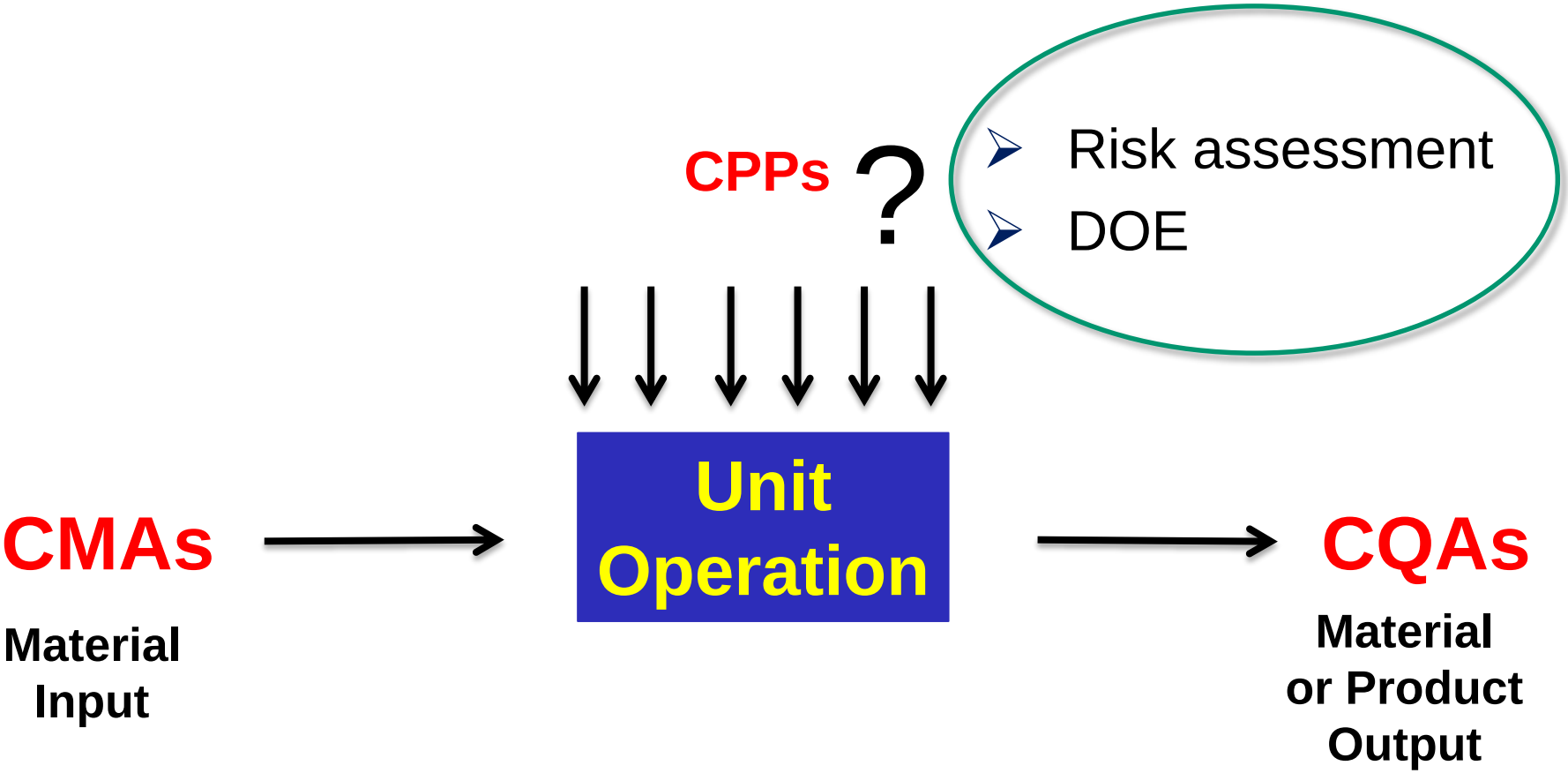


Quality Attributes Generally Observed in Biopharmaceutical Proteins

Product-Related Impurities and Substances	Process-Related Impurities	Contaminants
Aggregation	Residual DNA	Adventitious agents (bacteria, mycoplasma, fungi, and viruses)
Fragmentation	Residual host cell proteins	Endotoxins
C- and N-terminal modifications	Raw material-derived impurities	
Oxidation		
Deamidation/Isomerization		
Glycosylation (N-linked) Site occupancy Galactosylation Sialylation Fucosylation Oligomamnose forms Bisecting GlcNAc		
Glycosylation (O-linked)		
Glycation		
Conformation		
Disulfide bond and modifications/free thiols		
GlcNAc, N-acetylglucosamine		

Eon-Duval et al., Biotechnol. Progr., 2012

CMA/CPP/CQA Relationship



$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

RISK ASSESSMENT

Typical MAb manufacturing process involves

> 20 distinct unit operations
> 200 process parameters
> 50 raw materials

→ ***Prioritization***

Who?

Multidisciplinary team of representatives from:

quality
process development
regulatory
Manufacturing
analytical groups

→ Failure mode and effect analysis (FMEA) → Risk Priority Number (RPN)

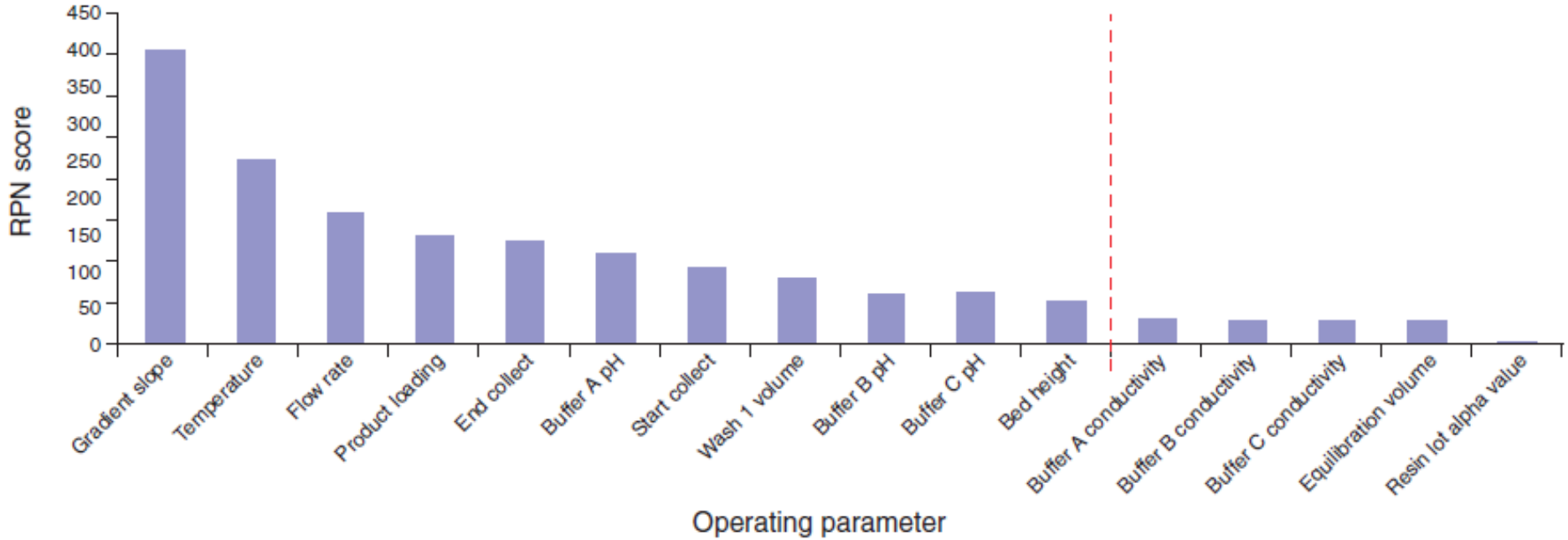
How?

Using data and knowledge from:

previous development
platform process knowledge
literature

Banerjee A., BioPharmInt, 2010

Chromatographic step (Downstream process)

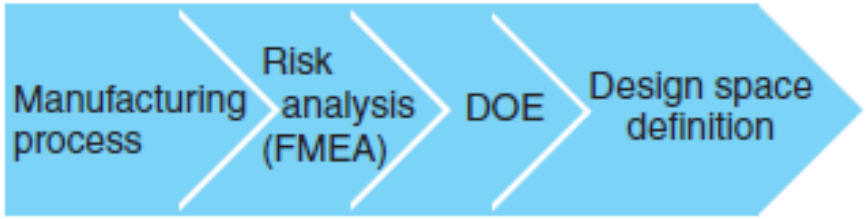


Pareto chart showing RPN scores for the operating parameters for a chromatography step in a biotech process. Parameters that had RPN scores higher than the cutoff (RPN = 50) were further examined in process characterization

Rathore S., Winkle H., Nature Biotech 2009

QbD and DoE

- A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches
  - This understanding can be gained by application of, for example, ***formal experimental designs***, ***process analytical technology (PAT)***, and/or prior knowledge
  - Appropriate use of quality risk management principles can be helpful in prioritizing the additional pharmaceutical development studies to collect such knowledge
- As such, the QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD



Chromatographic step (Downstream process)

a

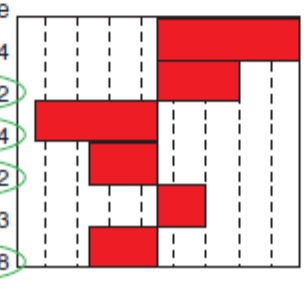
JMP Analysis	Scale estimate	*P* value	Scale estimate	*P* value
	Recovery percentage		Purity percentage	
Center point	61.12	Std 3.76	58.9	Std 0.9
Temperature	–16.26	<0.0001	6.15	<0.0001
Buffer A pH	–16.54	<0.0001	–4.2	<0.0001
Buffer B pH	12.9	0.0003	–3.25	0.0004
Loading	–13.05	0.0003	2.2	0.0087
Flow rate	9.495	0.0044		
Bed height	–6.955	0.0289		
Gradient slope				
Start collect				
End collect			1.9	0.0207

Effect of significant magnitude

Statistically significant impact

b

Scale estimates



Term	Scale estimate	s.e.m.	*t* ratio	*P* > |*t*|
Intercept	58.906204	0.312877	188.27	<0.0001
Temp. (7, 13)	0.9851902	0.408857	0.2.41	0.0237
Buffer A pH (6,6.4)	–1.499674	0.384437	–3.90	0.0006
Buffer B pH (6,6.4)	–0.846512	0.425152	–1.99	0.575
Load rate (7,9)	0.5673823	0.369419	1.54	0.1371
Buffer B pH *load rate	–0.851518	0.476017	–1.79	0.0858

Rathore S., Winkle H., Nature Biotech 2009

DESIGN SPACE

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Chromatographic step (Downstream process)

Design space for case study involving characterization of a process chromatography step

Process parameter	Categorization	Operating range[a]	Acceptable range[b]
Temperature	Critical	10 ± 1 °C	10 ± 3 °C
Buffer A pH	Critical	6.2 ± 0.1	6.2 ± 0.2
Buffer B pH	Key	6.2 ± 0.1	6.2 ± 0.2
Flow rate	Key	0.08 ± 5% CV/min	0.08 ± 10% CV/min
Product loading	Key	8 AU/ml	7–9 AU/ml
Bed height	Key	18 ± 1 cm	18 ± 3 cm

[a]Operating ranges constitute the operating space for the process step. [b]Acceptable ranges define the process design space for the step. AU, arbitrary units.

Fed-batch production and virus inactivation

A Subset of the Operating Parameters and Their Associated Ranges Investigated During Process Characterization Studies for the Fed-Batch Production Culture and Virus Inactivation Step

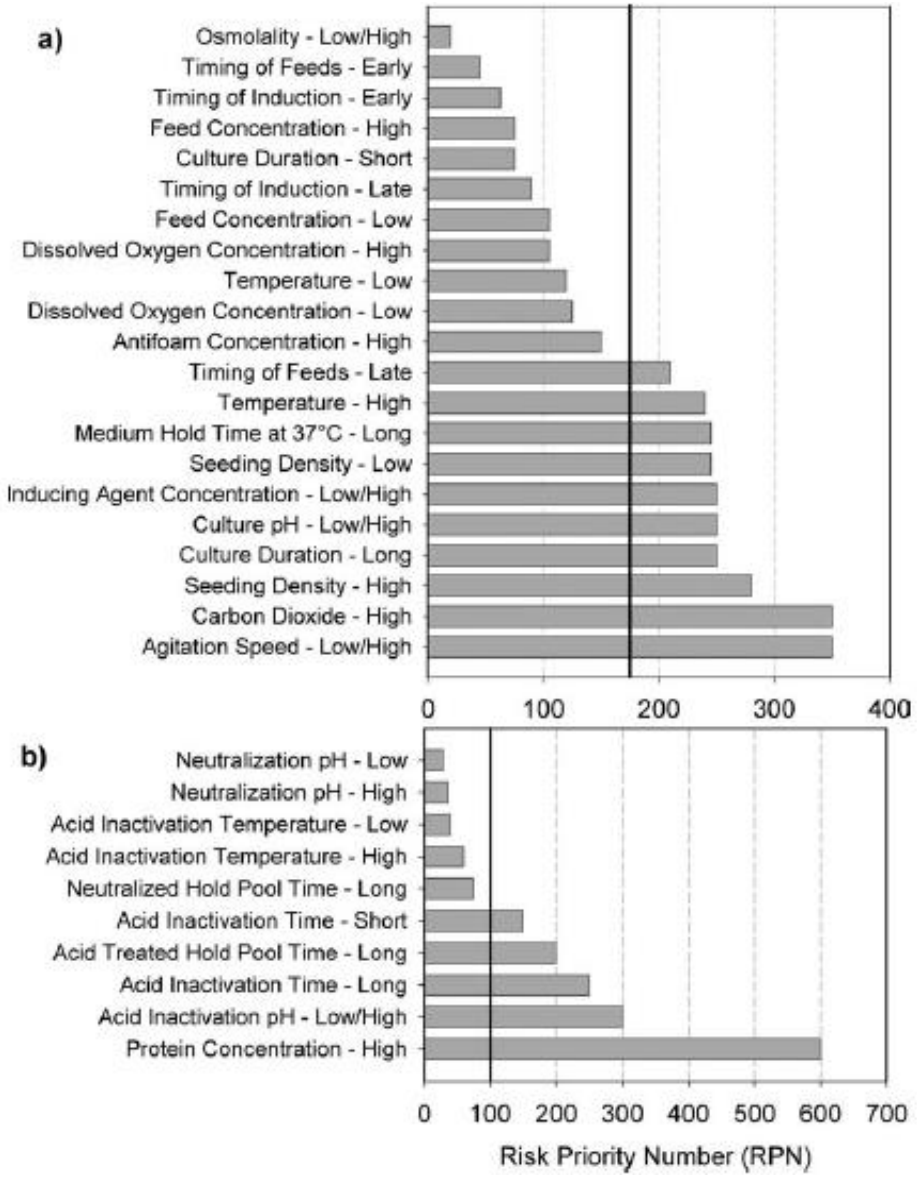
Operating Parameters	Test Range
Fed-batch production culture*	
Temperature (°C)	± 0.50
pH	± 0.13
Culture duration (hours)	± 24
Seeding density (10^6 cells/mL)	± 1.0
Timing of induction (hours)	± 4.0
Virus inactivation step**	
Inactivation temperature (°C)	15-30
Inactivation pH	3.5 – 4.1
Inactivation time (min)	60 – 180
Protein concentration (g/L)	2.2 – 5.5

The outlined test ranges are relative to the control set points

*** A half fractional factorial design was used to characterize the operating parameters for the production culture**

**** A central composite design was used for the virus inactivation step**

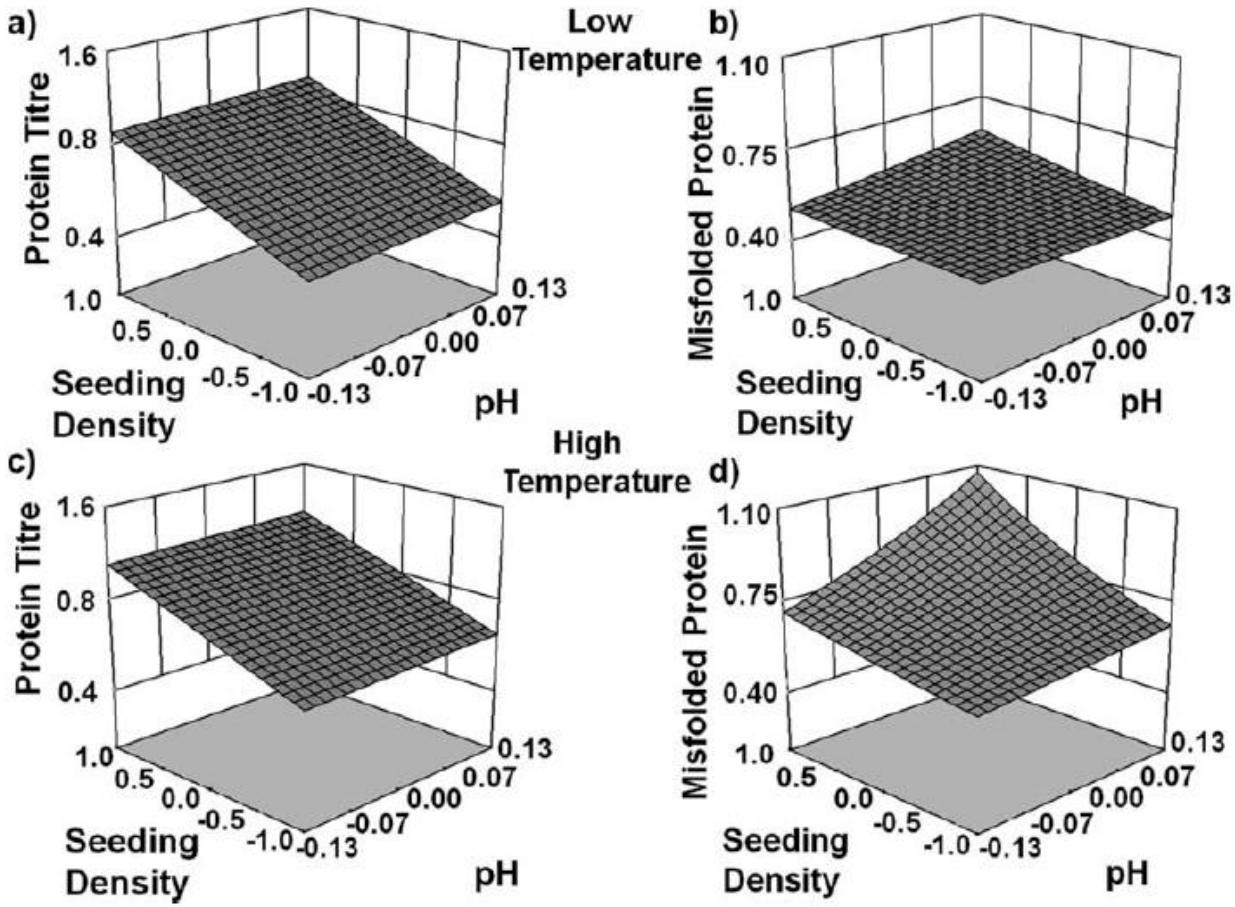
Looby M. et al., Biotechnol. Progr., 2011



Histograms of RPN values for operating parameters of (a) the fed-batch production culture and (b) the virus inactivation step. RPN values were determined using FMEA risk assessments and ranked in order of absolute magnitude.

The solid vertical lines represent RPN cut-offs of 175 and 100 for the fed-batch production culture and virus inactivation steps, respectively.

Looby M. et al., Biotechnol. Progr., 2011



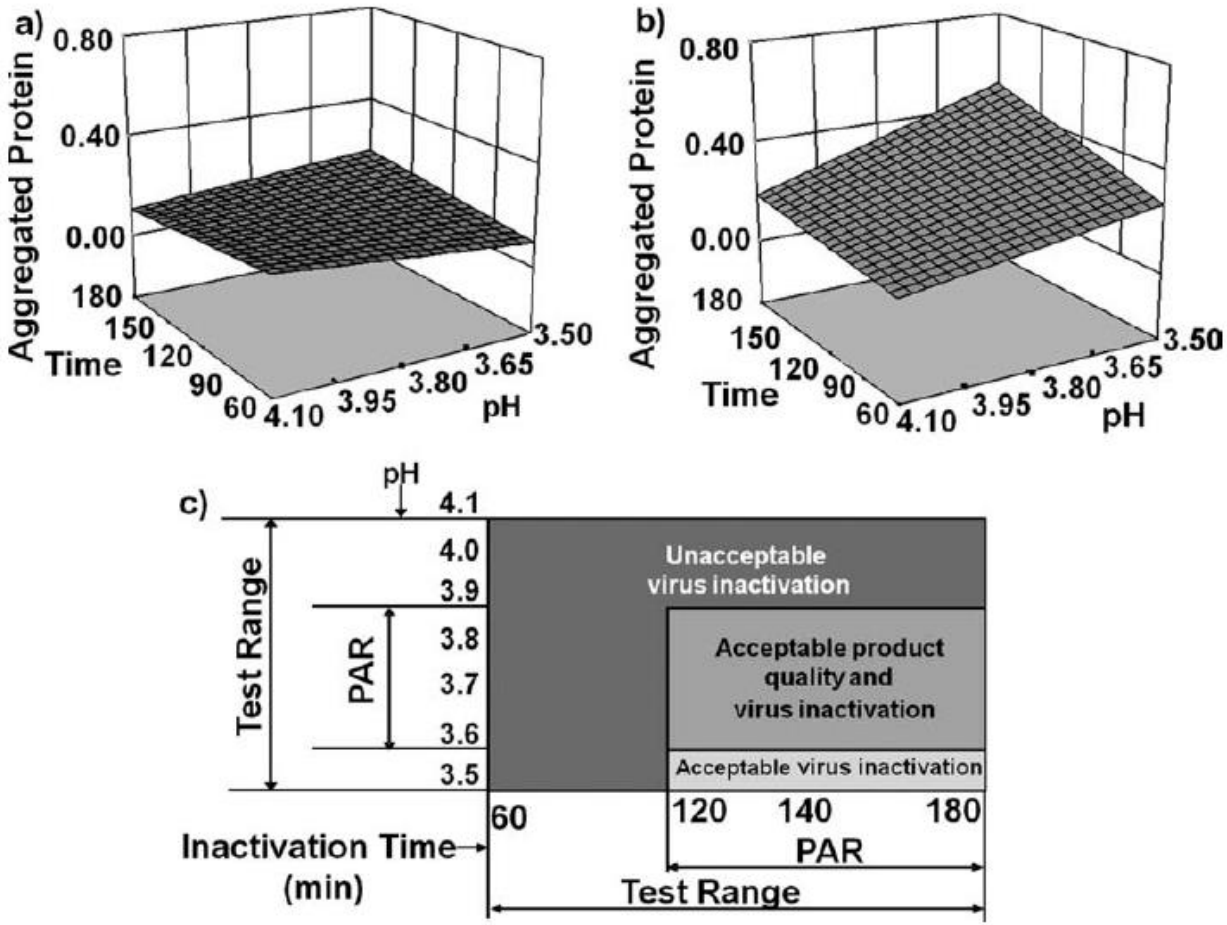
Impact of the three-factor interaction (pH x temperature x seeding density) in the fed-batch production culture.

Effects on protein titre (a, c) and levels of misfolded protein (b, d). Low (a, b) and high (c, d) temperatures are ± 0.5°C of the control setpoint. Levels of misfolded protein have been normalized with respect to the specification for this attribute, protein titres have been normalized with respect to the protein titre of the control, which was operated at mid-range conditions.

Looby M. et al., Biotechnol. Progr., 2011

Proven Acceptable Range:

A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria. (ICH Q8)

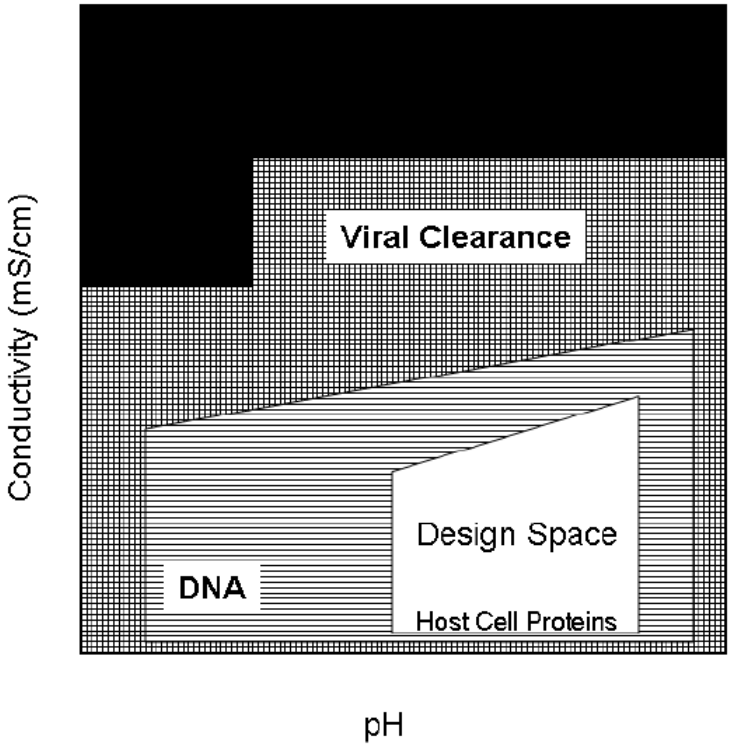


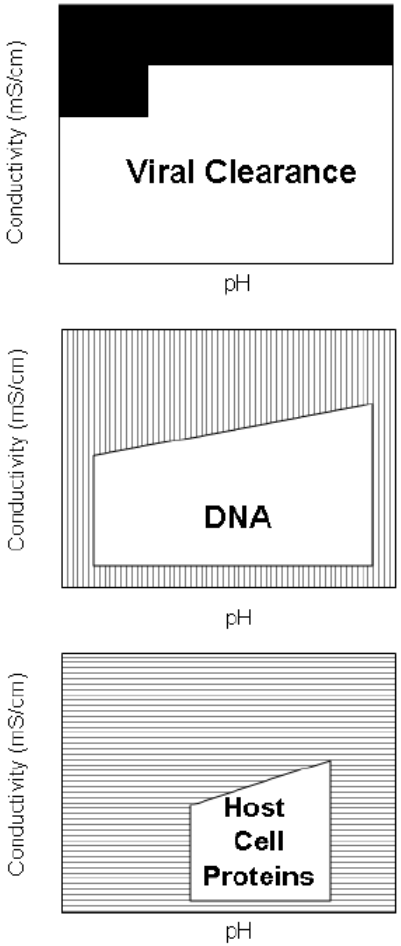
Impact of the two-factor interaction (pH x time) on the levels of protein aggregation during the virus inactivation step at a protein concentration of 5.5 g/L and at (a) 25°C and (b) 30°C

Looby M. et al., Biotechnol. Progr., 2011

10.3 Example 3: Presentation of a Design Space for a Biotechnology Drug Substance Unit Operation

This example is based on a design space for a drug substance purification unit operation (Q-anion exchange column run for a monoclonal antibody in flow-through mode), determined from the common region of successful operating ranges for multiple CQAs.





Viral clearance and Host Cell Proteins (HCP) ranges were derived from multivariate experimentation (see ICH Q8). The successful operating range for DNA was derived from prior knowledge (platform manufacturing) which in turn was derived from results of multivariate studies performed on related products.

ICH Q11

BIOLOGICALS

Drug Substance

Drug Product

ICH Q11

The considerations for design space addressed in ICH Q8 for an enhanced approach to the development of the drug product are applicable to drug substance.

In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.

Small molecules:

… Solubility

Bio-macromolecules:

… Stability !

Monoclonal Antibodies

- Monoclonal antibodies (MAbs) have gained significant attention in recent years because of their specificity towards a range of targets
- However, MAbs are usually low potency molecules and require several mg/kg body weight doses (a typical dose may range from 100 to 200 mg)
- Antibodies, like other proteins, are prone to a variety of physical and chemical degradation pathways
  - ✓ In many cases, multiple degradation pathways can occur at the same time and the degradation mechanism may change depending on the stress conditions
  - ✓ These degradation pathways are divided into two major categories, **physical** and **chemical** instabilities

MAbs: Liquid Formulations

- Liquid dosage form is usually preferable to lyophilized products as it is easier to administer and less expensive to manufacture
  - ✓ Among all the commercial antibody products, about half are stable enough to be formulated in a liquid form
- Formulating a successful liquid product needs consideration of **at least** the following aspects
  - ✓ Protein concentration (high concentrations → high tendency to aggregate during storage and likely high viscosity, leading to more difficulty during injection
  - ✓ Effect of formulation pH
  - ✓ Effect of buffering agents
  - ✓ Effect of formulation excipients/stabilizers (e.g., sugars)
  - ✓ Effect of shaking/shearing

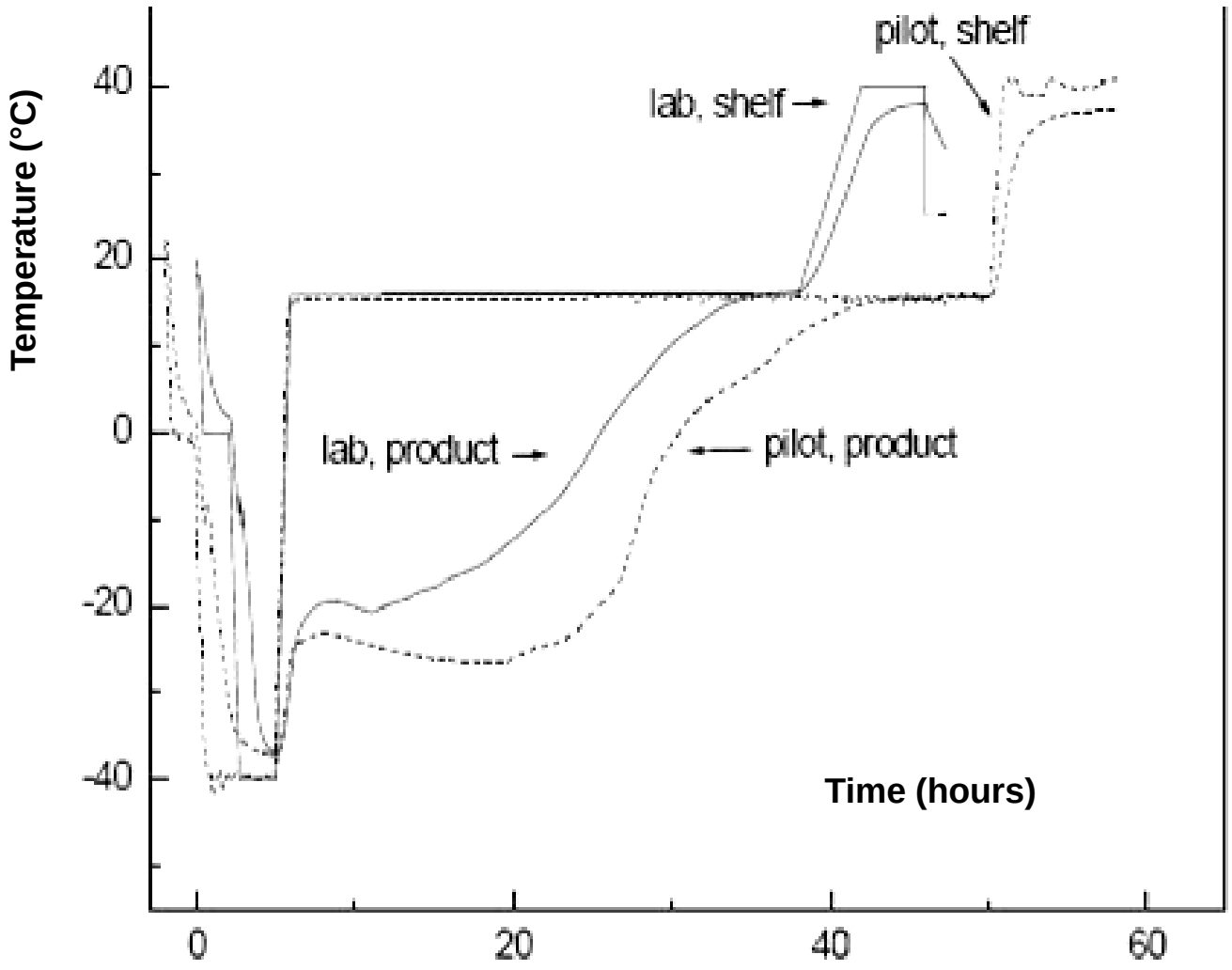
Formulation of Biopharmaceuticals

- Without lyophilization, nearly 50% of biopharmaceuticals including plasma, vaccines and antibodies could not be commercially available
- With a greater trend to outsource manufacturing and more biologicals requiring freeze-drying, this market is set to maintain its year-on-year double digit growth

MAbs: Lyophilized Formulations

- Like most proteins, some antibodies are not stable enough in a liquid form and lyophilized dosage forms will have to be considered
- Critical issues in formulating a lyophilized antibody product
  - ✓ Amorphous versus Crystalline state
  - ✓ Effect of formulation excipients
    - Mannitol and Glycine often used as bulking agents, however crystallization of these agents during lyophilization makes them wonderful bulking agents **BUT** poor stabilizing agents
  - ✓ Effect of buffering agents
    - Significant pH shift may be induced during lyophilization if a component of the buffer system undergoes selective crystallization (e.g., as sodium phosphate)
  - ✓ Protein concentration (many antibodies have been shown to be less stable both during lyophilization and storage at high concentrations)
  - ✓ Effect of moisture content

What happens if a start-up biotech company outsources the manufacture of the first clinical lot of a MAb and the CMO, due to lack of technical experience, decides to apply the same lyophilization cycle as that used by the start-up company during their lab-scale preliminary trials?



The batch fails!!!!!!!

Example of QTPP Elements for a Lyophilized Product (1/2)

QTTP Element	Requirement
Route of administration	IV infusion (slow)
Dosage Strength	100 mg/vial
Presentation	Single dose
Solution for reconstitution	10 mL SWFI, then to be diluted with 100 mL normal saline (provided by the pharmacy)
Concentration after primary reconstitution	10 mg/mL
Container Closure System	20R glass vial, rubber stopper, meets pharmacopoeial requirements for parenteral dosage forms
Composition	Precedented and safe Inactive Ingredients
Shelf life	Two years at 2°-8°C
Stability during administration	Reconstituted solution is stable for 24 hours at temperature ≤ 30°C

Example of QTPP Elements for a Lyophilized Product (2/2)

QTTP Element		Requirement
Drug Product Quality Attributes	Appearance	Meets pharmacopoeial requirements for parenteral dosage forms as well as product specific requirements
	Identification	
	Assay	
	Uniformity of Dosage Units	
	Related Substances	
	Water Content	
	Residual Solvents (if relevant)	
	Sterility	
	Bacterial Endotoxins	
	Reconstitution time	
	pH and Appearance of reconstituted solution	

Lyophilized Formulation: CMAs/CPPs/CQAs

INPUTS (potential material/formulation quality attributes)

Fill volume

Solution concentration

Assay

pH

Type of bulking agent

……..

……..

PROCESS PARAMETERS (pre-determined)

Shelf T°C during freezing

Shelf T°C during sublimation

Chamber pressure

Shelf T°C during 2ary drying

Condenser T°C

Process Operation

LYOPHILIZATION

Pre-cooled shelves

Tray lyophilization

Start of primary drying

Process controls

Uniformity of content

Assay

Impurities

Residual moisture

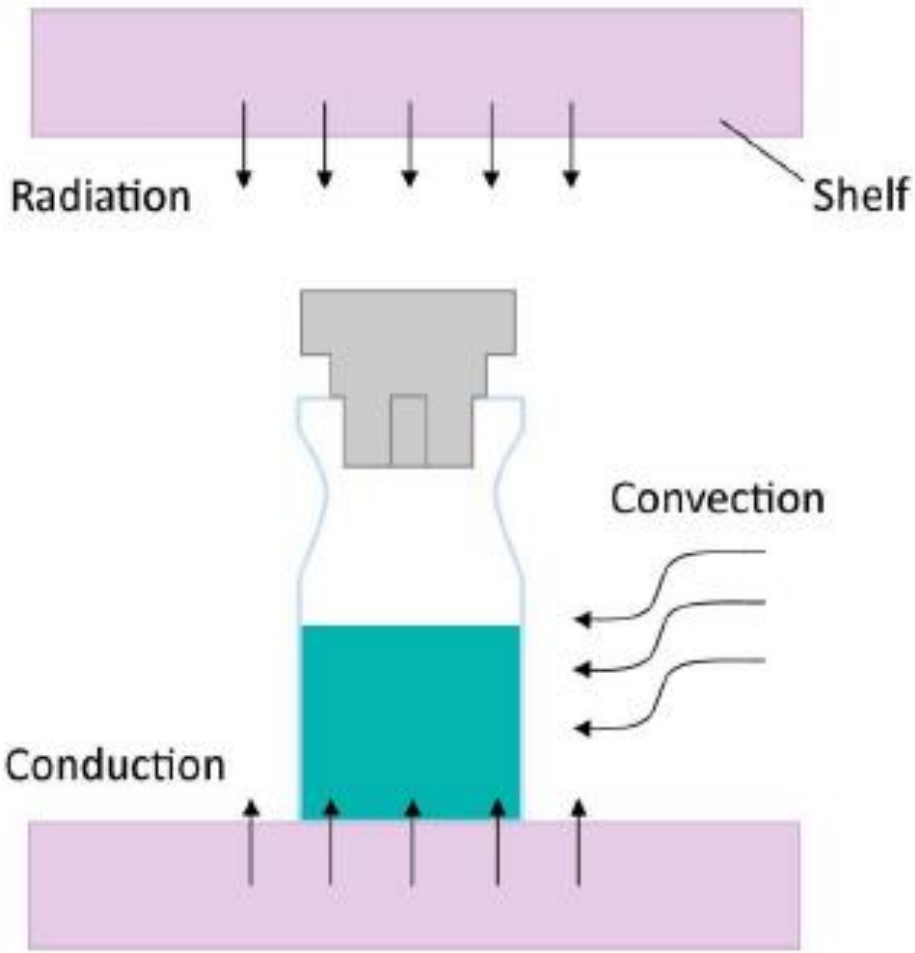
Reconstitution: time, appearance, pH

……..

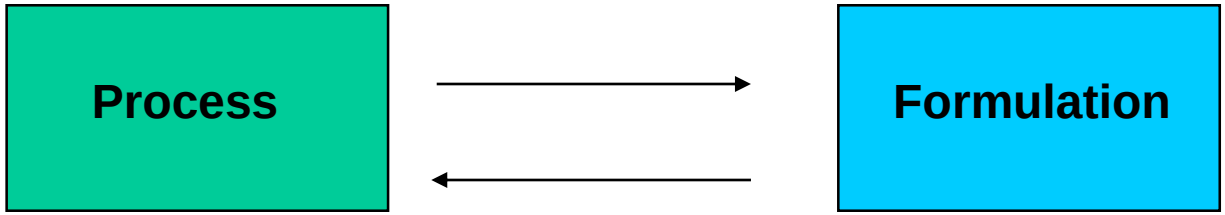
OUTPUTS (potential Drug Product quality attributes)

Critical Process Parameters (CPPs)

- Product temperature (T_p) should be maintained below formulation critical temperature during sublimation
- T_p, per se, **IS NOT** a CPP, **BUT** is influenced by
  - ✓ Shelf temperature
  - ✓ Chamber pressure
- Other inputs include
  - ✓ Vial size, heat transfer
  - ✓ Fill depth
  - ✓ Concentration



Formulation and Process

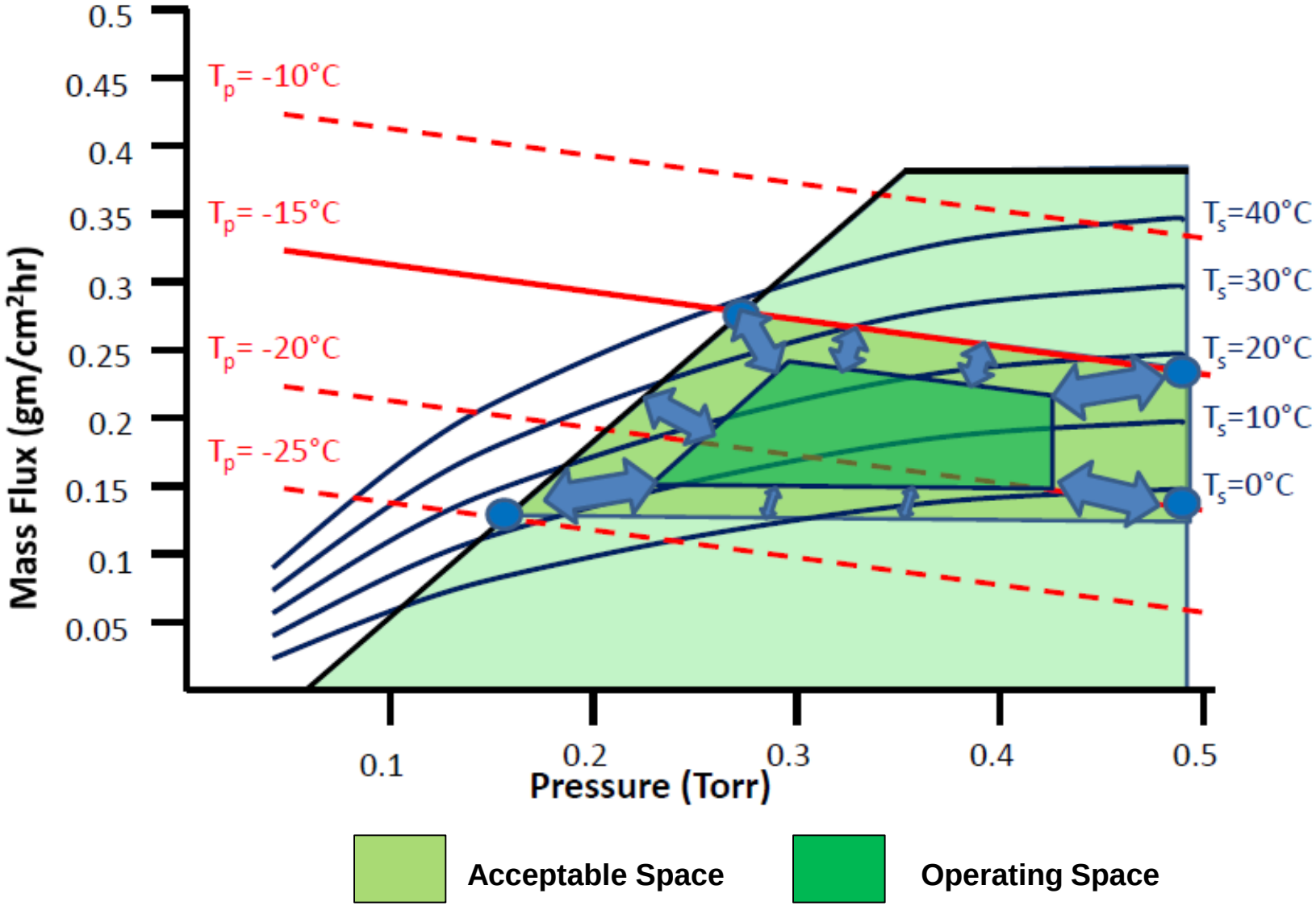


- **Formulation Determines Process**
  - ✓ T_g' and Collapse
    - Low T_g' means low temperature and <u>long</u> process
  - ✓ Product Resistance to mass transfer
    - High solids content means long process
- **Process may Determine Formulation Properties (i.e., T_g' and T_g)**
  - ✓ Crystallization may depend on freezing process
    - Incomplete crystallization of bulking agent and/or salts depress T_g'

Lyophilized Formulation: QbD

- Prior knowledge
- **QTPP**
- Formulation identification and characterization (thermal “fingerprint”)
- **CMAs – CPPs – CQAs**
  - ✓ Initial risk assessment followed by experimentation with multivariate studies ⇒ Identification of robust process conditions and their acceptable limits
- **Final overall risk assessment** (e.g., independent evaluation of each CQA and Failure Mode and Effects Analysis (FMEA) to assess the severity of the failure, the probability of CQA going out of the acceptable range, and ability to detect it based on proposed in-process and lot release testing
- Based on the scoring the proposed overall **Control Strategy** is refined to ensure the CQAs are within the acceptable ranges
  - ✓ **PAT in lyophilization**: MTM (Manometric Temperature Measurement), TDLAS (Tuner Diode Laser Absorption Spectroscopy), NIR (Near Infrared Spectroscopy), wireless product probes, Pirani vs CM (Capacitance Manometer) pressure
- Construction of the **Design Space** (the most challenging part!)

Building a Design Space



Lyophilization of Proteins: Conclusions

- "Good Freeze Drying Practice" for Proteins
  - ✓ Formulation
    - The level of buffer should be minimized to avoid buffer crystallization and pH shift during freezing and to avoid significant reduction of T_g'
    - The T_g of the freeze-dried formulation should be significantly higher than the shipping and storage temperatures
    - Stabilizers are normally required (sucrose or trehalose)
  - ✓ Process
    - Control the ice nucleation temperature during freezing, control product temperature below the collapse temperature during primary drying, slow shelf ramp to secondary drying

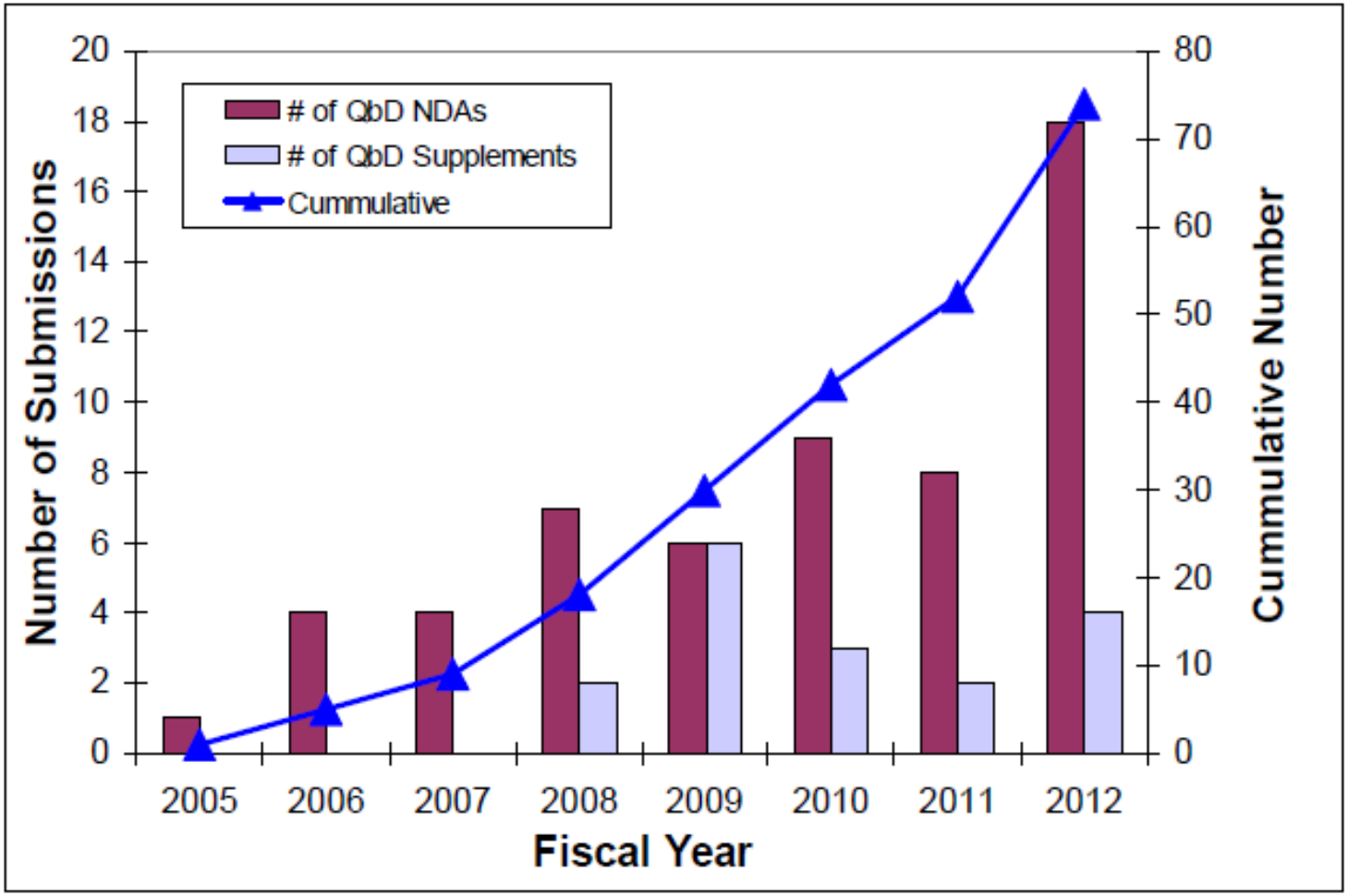
FDA and QbD Implementation in the Generic Industry

- It was **"strongly encouraged"** (Jan 2013) that the following 5 elements **all** be present in all ANDA filings:
  - ✓ QTPP
  - ✓ CQAs of the Product
  - ✓ Product Design/Understanding
  - ✓ Process Design/Understanding
  - ✓ Product and Process Control Strategies
- Though there is no written mandate, the general industry practice is to accept this

EMA and QbD

- The Agency welcomes applications that include quality-by-design aspects
  - ✓ These can include applications for **marketing authorization**, **variations to existing marketing authorizations** and **scientific advice**
- The "pilot programme" for the **parallel assessment** launched by EMA and FDA in 2011 was extended for a further two years as of 1 April 2014
  - ✓ Participation in the pilot is voluntary
  - ✓ Interested applicants and sponsors should notify both agencies **three months prior to submission** of an application
  - ✓ The evaluation is performed separately by each agency, with regular communication and consultation throughout the review
    - The aim is a common list of questions to the applicants and harmonized evaluation of their responses

Count of QbD-based Applications



S. P. Miksinski (FDA), AAPS 2012 Conference
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341173.pdf

Biotech QbD Applications

- Currently a reality
- Perjeta™ (Pertuzumab) BLA submitted in 2011
  - ✓ FDA Pilot for Biologics
  - ✓ FDA and EMA conducted a collaborative review of the submission
  - ✓ QbD-based Control Strategy approved globally
  - ✓ US and EU did not approve Design Space
- Gazyva ™ (Obinutuzumab) BLA submitted in 2013
  - ✓ Lessons learned from Perjeta taken into the filing
  - ✓ FDA, EMA and many other global Health Authorities have approved both the QbD-based Control Strategy and Design Space

Benefit for Industry

- **From Product and Process Understanding**
  - ✓ More robust process
  - ✓ Opportunity to improve yield
  - ✓ Reduced failure rate
  - ✓ Reduced number of recalls
  - ⇒ **More predictable supply**
  - ⇒ **Reduced out of stock situation**
- **From Opportunities (DS and RTRT)**
  - ✓ Continuous quality verification
  - ✓ Process monitoring in real time
  - ✓ Reduced batch cycle time
  - ✓ Reduced final product testing
  - ⇒ **Patient benefit!**

DS: Design Space
RTRT: Real Time Release Testing

Grazie a tutti per l'attenzione!

Approfondimenti, richieste:

m_adami@alice.it

mariacristina.bonferoni@unipv.it