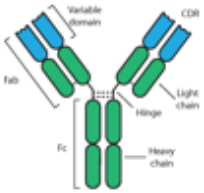


Workforce of the Future

UCDAVIS
UNIVERSITY OF CALIFORNIA

Guest Lecture: Biologics Quality by Design (QbD)

Meli Gallup – Genentech – Director Global MSAT Biologics Drug Products
Rosalina Padilla – Grifols – Director Quality Assurance
Ryan Chaney – Genentech – Senior Engineer Global MSAT Drug Substance
Nassim Farrokhzad – AstraZeneca – Associate Principal Scientist Drug Product & Combination Products

Wednesday 25 May 2022 11 – noon PDT

Lecture Outline

Background

Quality by Design (QbD) in Biologics

Summary

Questions and Answers with Panelists

Workforce of the Future (WoF) Collaboration with UC Davis

Issue

Projected skilled US workforce gap in Biopharma in the next 5 – 10 years

Scope

- Process Development
- Manufacturing Operations

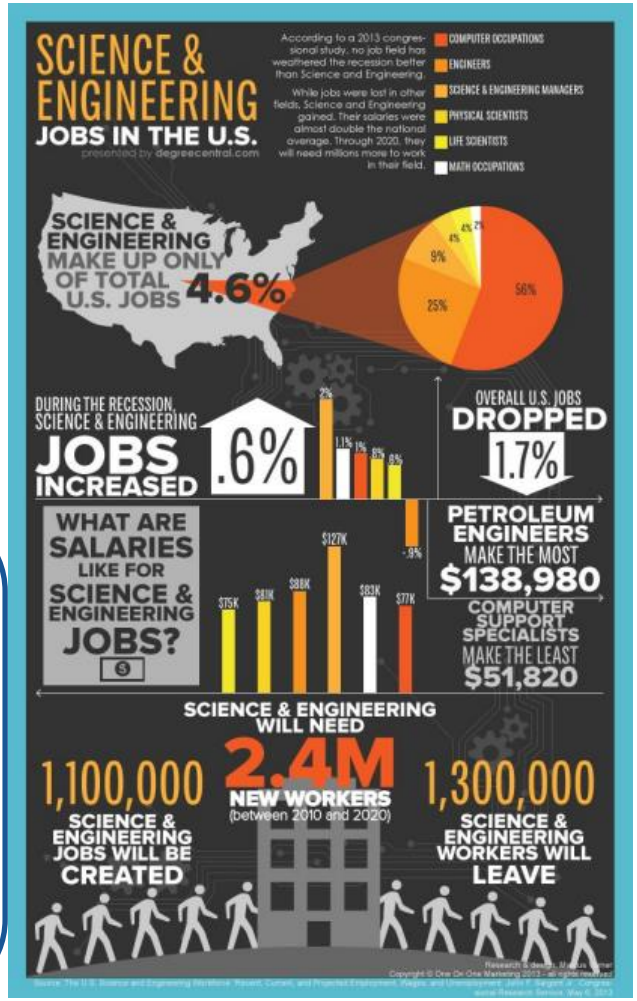
The End in Mind

- Biotech Process Engineer
- Process Development Scientists
- Combination Products Engineer
- Increase understanding technology, regulatory science, industry 4.0

Industry course focus area with universities in US.

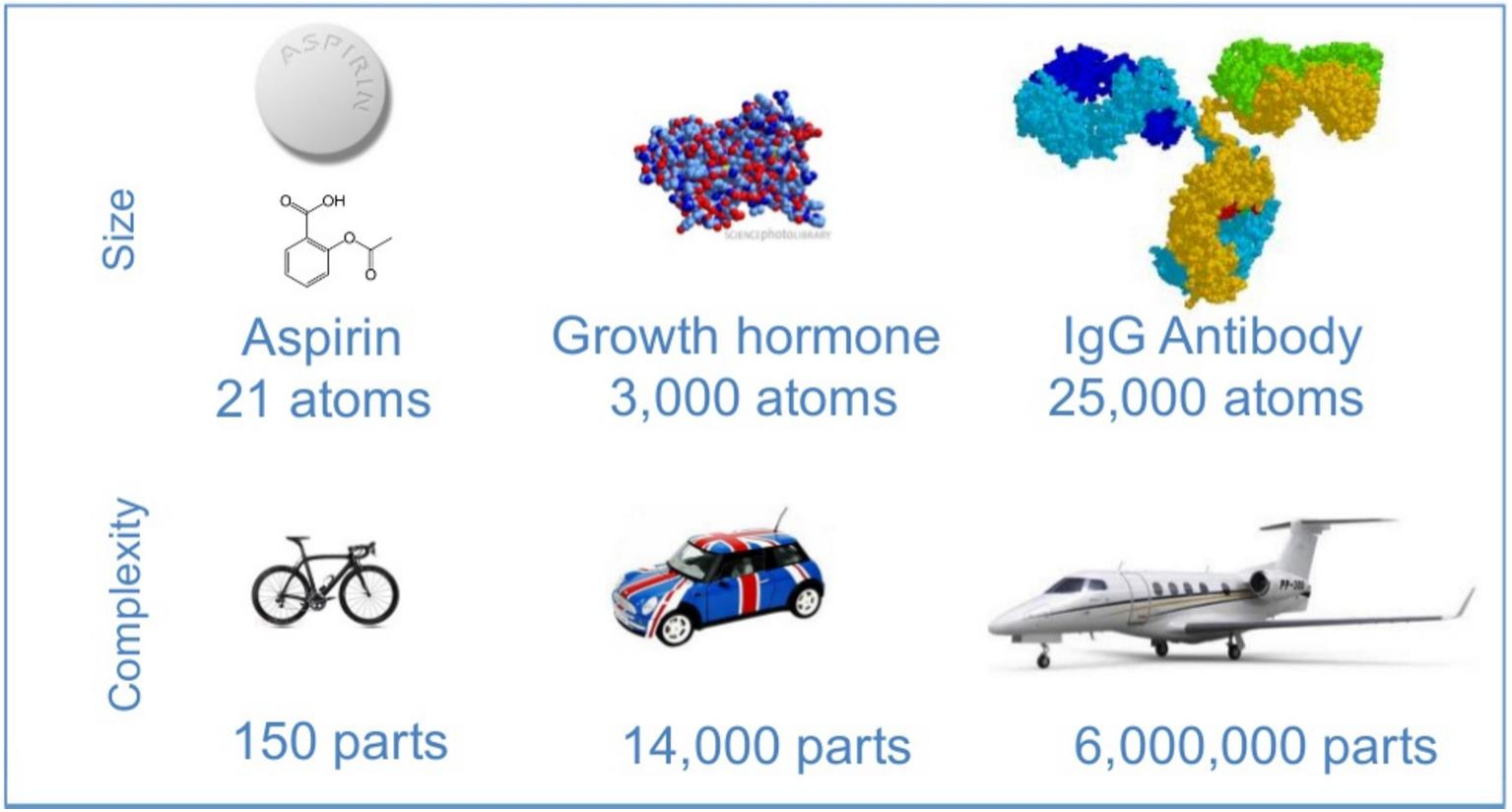
For UC Davis:

- QbD lecture
- Pharmaceutical Risk Management course
- IT/Data Management course



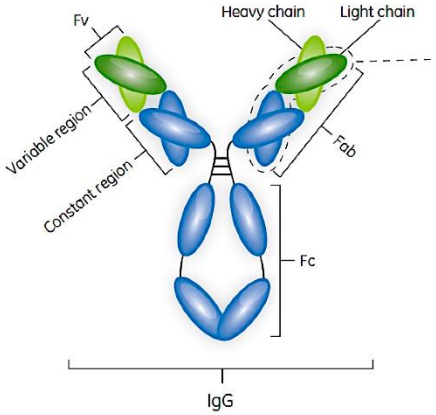
Biologics Manufacturing – How Hard Can It Be?

How do monoclonal antibodies differ from traditional chemical molecules?

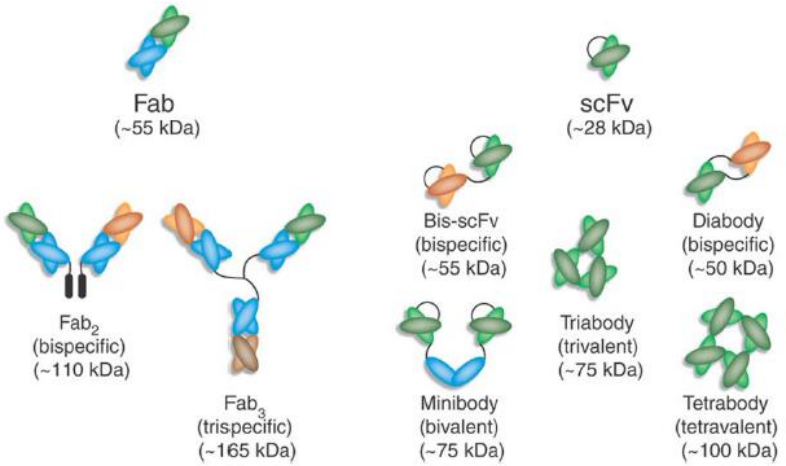


http://www.slideshare.net/bathasu/the-chemistry-of-monoclonal-antibodies

Monoclonal Antibodies



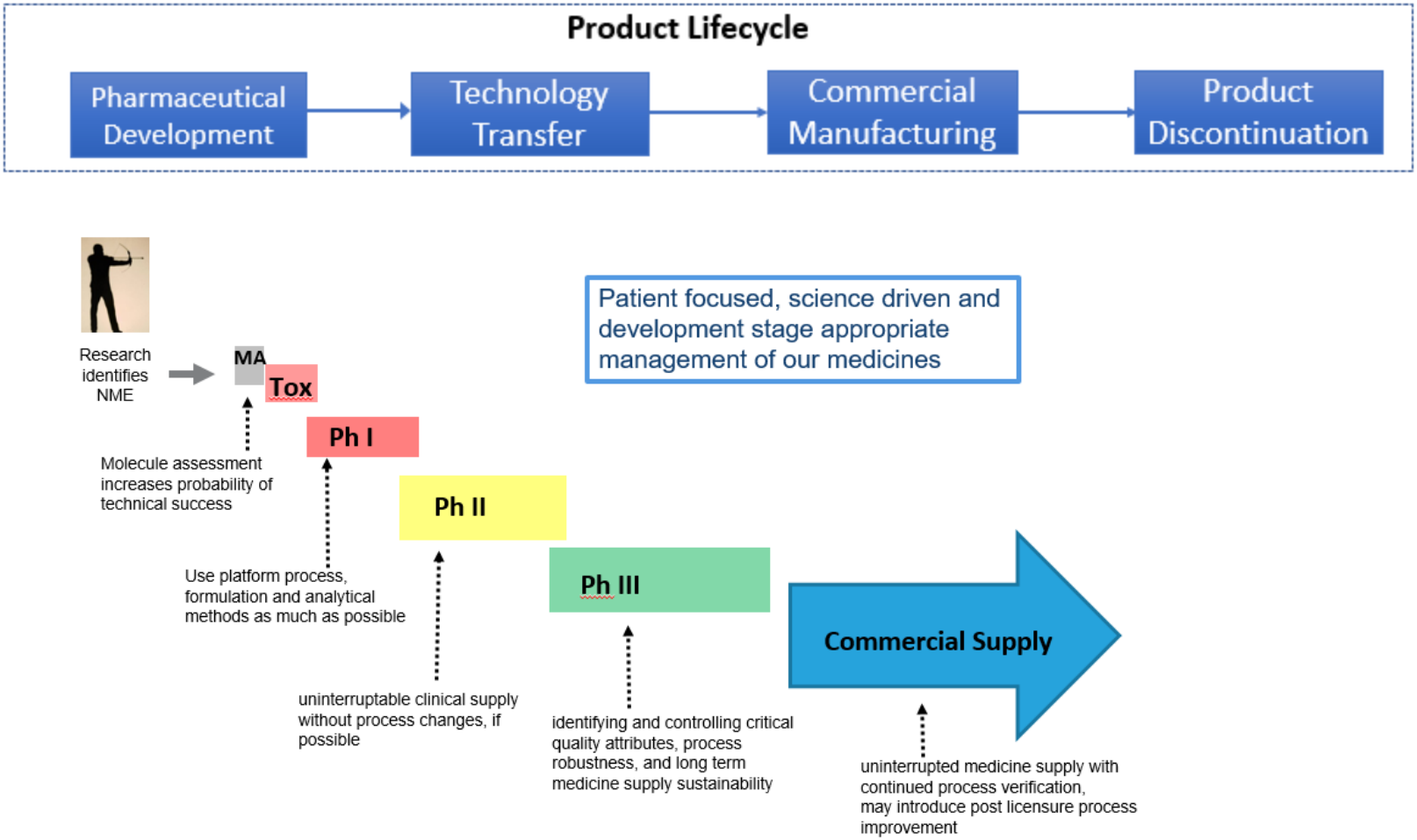
Rodrigo et al., 2015. Antibodies. 4: 259-277.



Shukla, et al., 2017. Bioengineering & Translational Medicine. 2: 58-69.

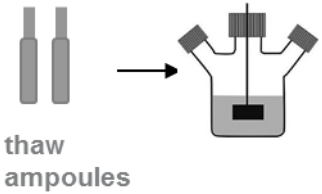
- mAbs are Y-shaped multi-domain protein molecules comprised of two light chains and two heavy chains linked by a series of disulfide bonds
- The fragment crystallizable (Fc) region binds to protein A
- Biotech is moving into novel antibody constructs

Product Lifecycle and Process Development Timeline



Illustrative Biologics Manufacturing Overview

Seed Train → Cell Culture → Harvest



Purification → Fill and Finish → Product to Patients

Lecture Outline

Background

Quality by Design (QbD) in Biologics Manufacturing

Summary

Questions and Answers with Industry Panel

Quality By Design

What Does Quality by Design Mean to You ?

Note: prepare word cloud

ICH and Quality by Design (QbD)

International Council (Conference) on Harmonization of Technical Requirements for Pharmaceuticals for Human Use

- A joint initiative between regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals
- Mission is to achieve to achieve greater harmonization worldwide to ensure safe, effective, and high quality medicines are developed, registered, and maintained in efficient manner while meeting high standards
- Outputs: ICH guidelines

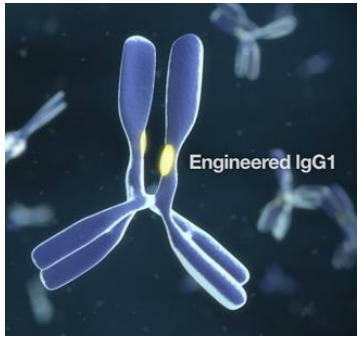
ICH Guidelines containing QbD elements:

- Q8 (R2) : Pharmaceutical Development
- Q9 : Quality Risk Management
- Q10 : Pharmaceutical Quality System
- Q11 : Development and Manufacture of Drug Substance
- Q12 : Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

What is Quality by Design (QbD)?

ICH Q8: QbD is 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**.

Leverages knowledge of structure-function relationship to define product attributes that are important



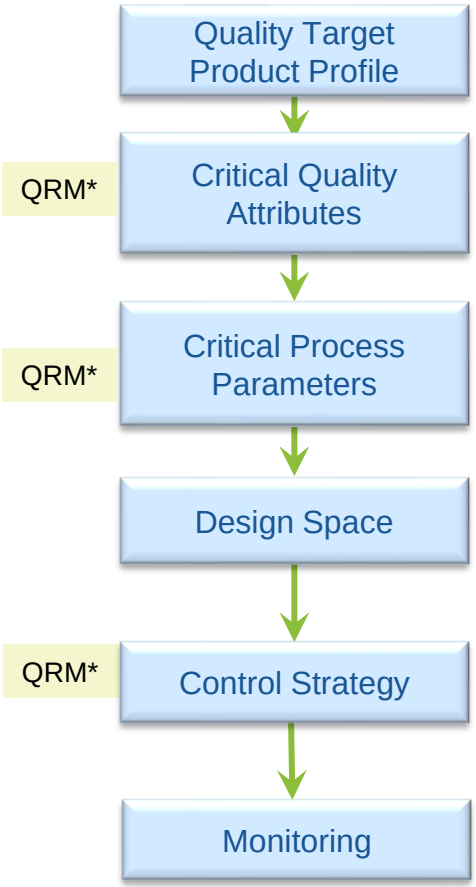
What are advantages of QbD?

- Expects a science-based and risk-based approaches to define the commercial manufacturing process
- Promotes deeper product & process understanding throughout the lifecycle of a product
- Allows framework for post-approval process changes

→ QbD does not change the manufacturing process in itself !

*ICH Q8 R2 - Pharmaceutical Development

QbD Elements – Framework Begins with the End in Mind



- **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.
- **(p)CQA** – A physical, chemical or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality (*(p) = potential*). **Considers the relevant Mechanisms of Action.**
- **(p)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 (*(p) = potential*).
- **DS** – The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- **CS** – A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

***QRM** – A systematic process of organizing information to support decision making based on identification of hazards and evaluation of risks management associated with those hazards.

Quality Target Product Profile

What are our target product quality characteristics to ensure safety and efficacious drug product?

Examples of elements for considerations:

- Target Product Profile: Therapeutic area, patient population
- Clinical Development: Route of administration (oral, IV, IM, SC), Clinical setting (self or clinic administration), Pharmacokinetic characteristics, Dosage form: liquid for injection, solid tablet, etc
- Legal requirements
- Quality characteristics: sterility, purity, etc

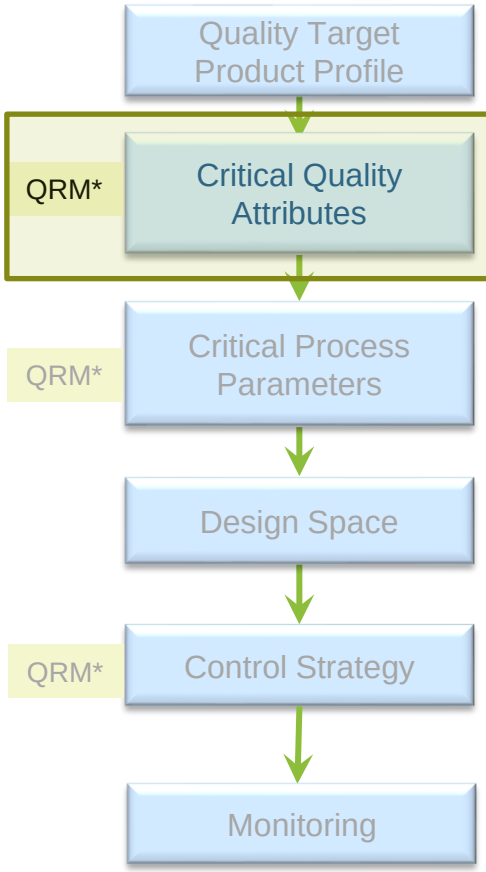
- Many others ..

Assessment Check

What are key characteristics of a Quality Target Product Profile?

A. Process Development and Platform Knowledge
B. Any attribute that can help with understanding drug product quality characteristics
C. Not relevant for biologics manufacturing
D. Process Development, Platform Knowledge, Product Understanding, Scientific Literature

QbD Elements – Framework Begins with the End in Mind



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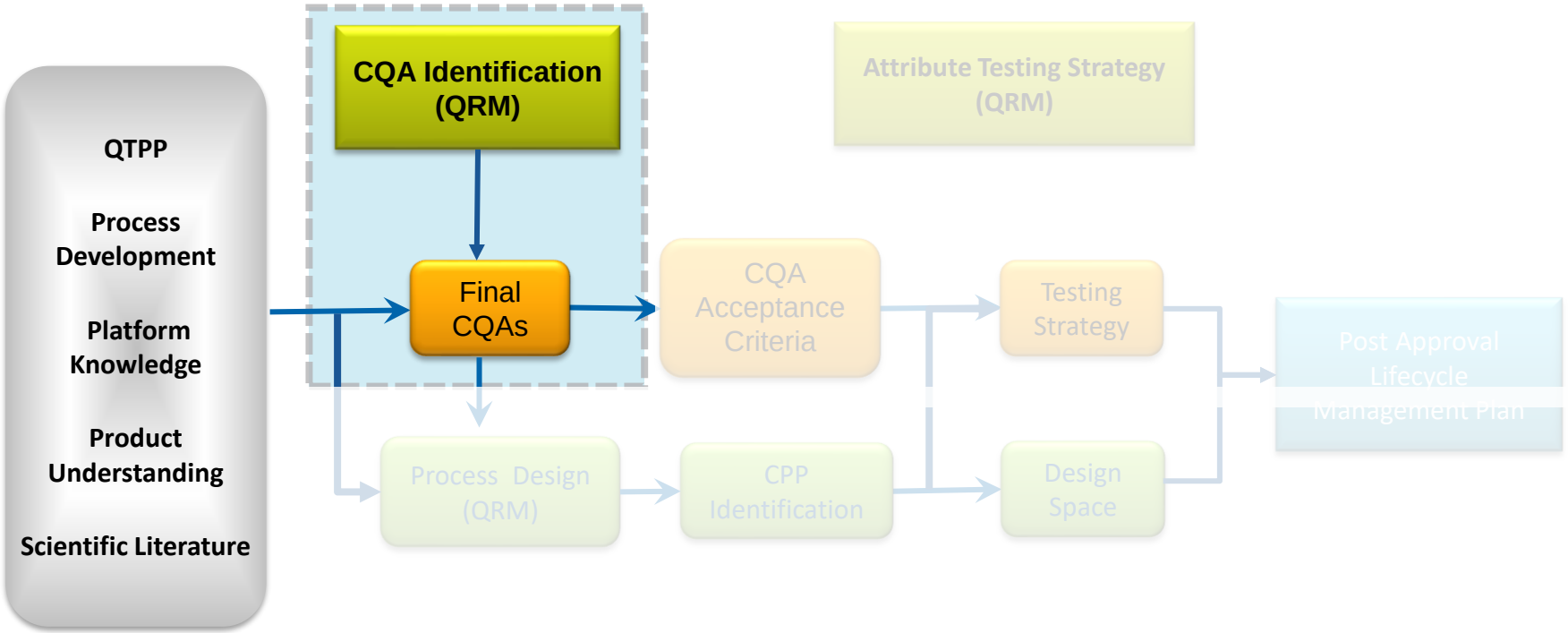
Quality Target Product Profile

QbD risk assessment tools assess product quality attributes for criticality

What attributes should be measured?

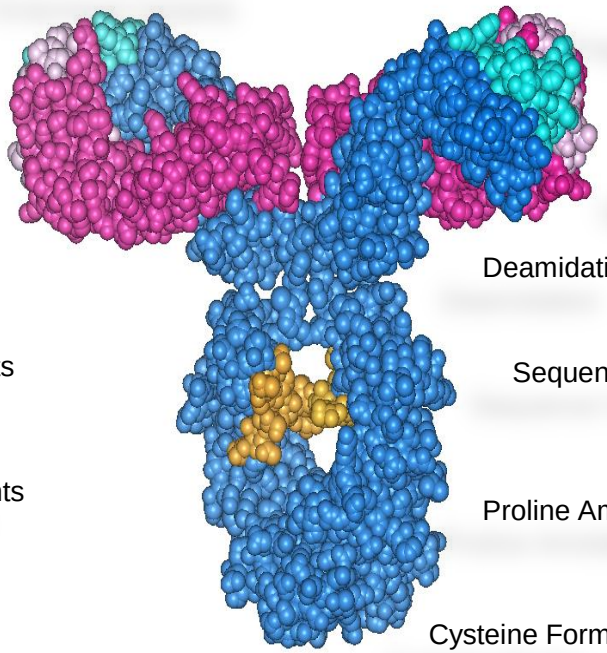


Critical Quality Attributes

What are potential Critical Quality Attributes for a Monoclonal Antibody?

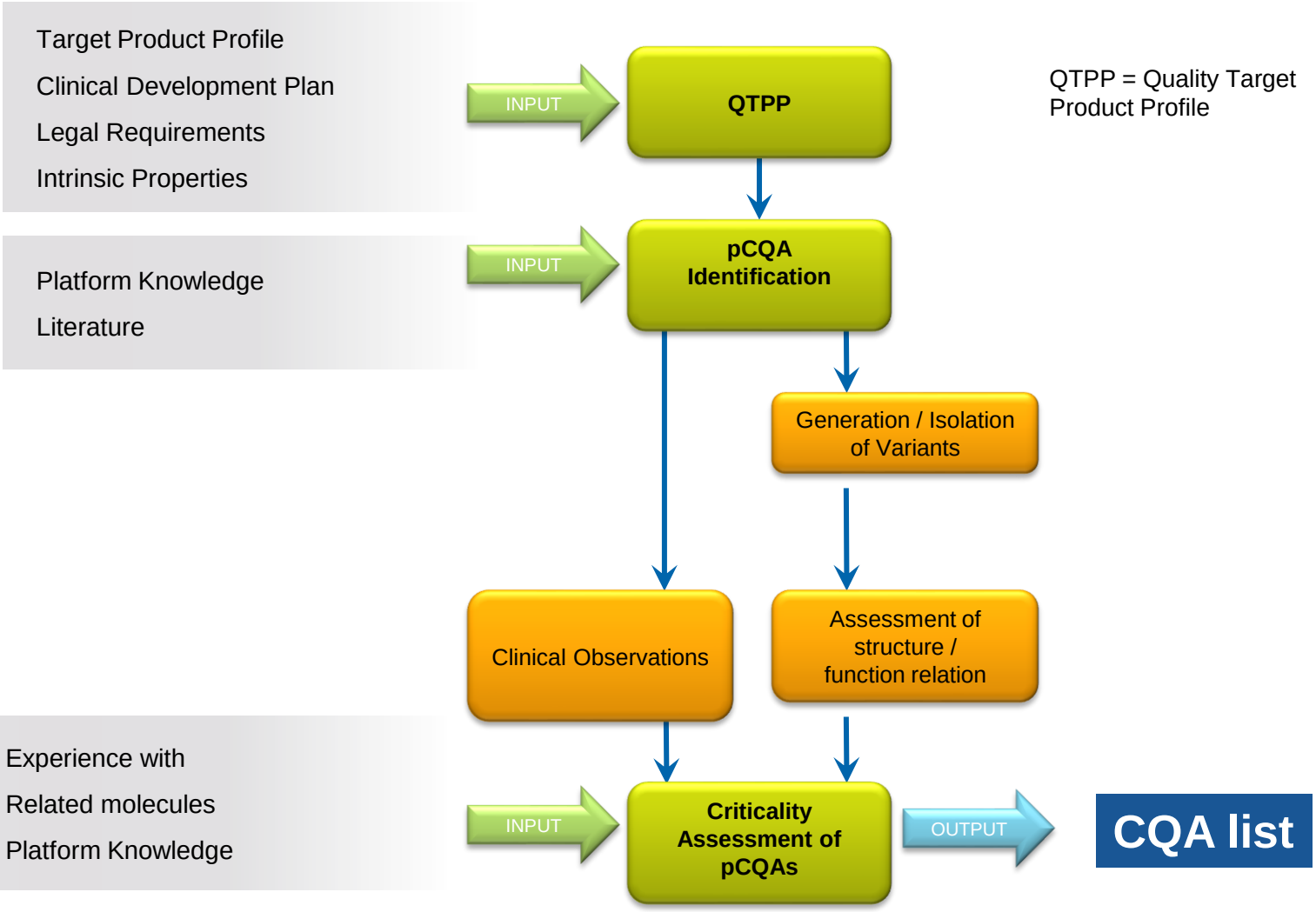
ICH Q8 R1: Critical Quality Attributes - Link Directly to Patient Safety & Efficacy

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**.



Critical Quality Attributes

Assessment Workflow



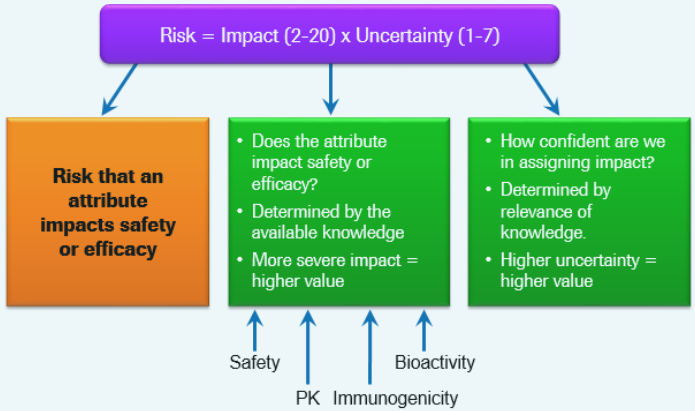
Critical Quality Attributes

Assessment Process

Categorize

Category	Assessment	Rationale for Approach
Product Variants	**Risk Ranking and Filtering**	Impact to patient safety and product efficacy is specific to variant in question, mechanisms of action, route of administration, etc.
Process-related impurities	**Risk Ranking and Filtering**	Clinical data from similar products can be used to assess safety
Composition and Strength	Obligate CQA	Potentially high impact to safety and efficacy
Adventitious Agents	Obligate CQA	Potentially high impact to safety
Raw Materials	**Compare Estimated Daily Intake and Acceptable Daily Exposure**	Extensive data available from safety and toxicity studies

Assess risks (QRM) (assign severity and uncertainty scores)



Summarized Outcomes

Product Variants	Process-Related Impurities	Obligatory CQAs
Size-Related Variants	Host cell protein	Adventitious Agents
HMWS	Host cell DNA	Virus
LMWS	Leached Protein A	Microbiological purity (bioburden, mycoplasma, leptospira)
Charge-Related Variants (Acidic)	Raw materials	Bacterial endotoxins
Glycation in CDRs		Drug Substance and Drug Product Composition and Strength
Oxidation-Related Variants		Protein content
Oxidation in CDRs		Osmolality
Oxidation at Met253 (homodimer)		pH
Structural Variants		Appearance (color, opalescence, and clarity)
Cysteine forms		L-histidine content
N316K sequence variant		Sucrose content
		Polysorbate 20 content
		Drug Product – Specific
		Subvisible particles
		Visible particles
		Extractable volume
		Sterility
		Container closure integrity

Abbreviations: CDR = complementarity-determining region; CQA = critical quality attribute; HMWS = high-molecular-weight species; LMWS = low-molecular-weight species.

Assessment Check

Which best describes the definition of Quality?

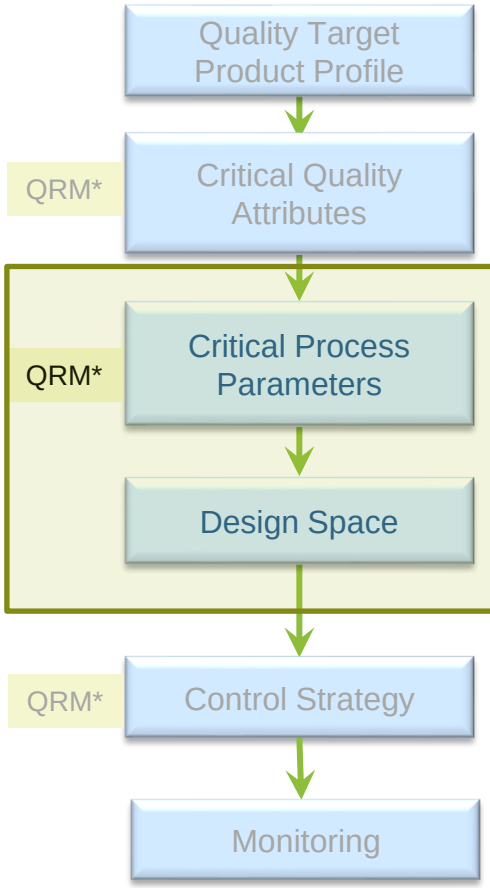
A. The degree to which a product passes its final QC testing specification
B. The degree to which a product complies with the FDA requirements
C. The degree to which a set of inherent properties of a product, system, or process fulfills requirements
D. The degree to which the term Quality is added to Standard Operating Procedures

Assessment Check

What is a Critical Quality Attribute?

A. Property or characteristics within appropriate range to achieve desired product quality
B. Summary of intended drug product quality characteristics
C. An attribute that is described as having critical quality
D. It is not important in the manufacturer of biologics products

Critical Process Parameters and Design Space



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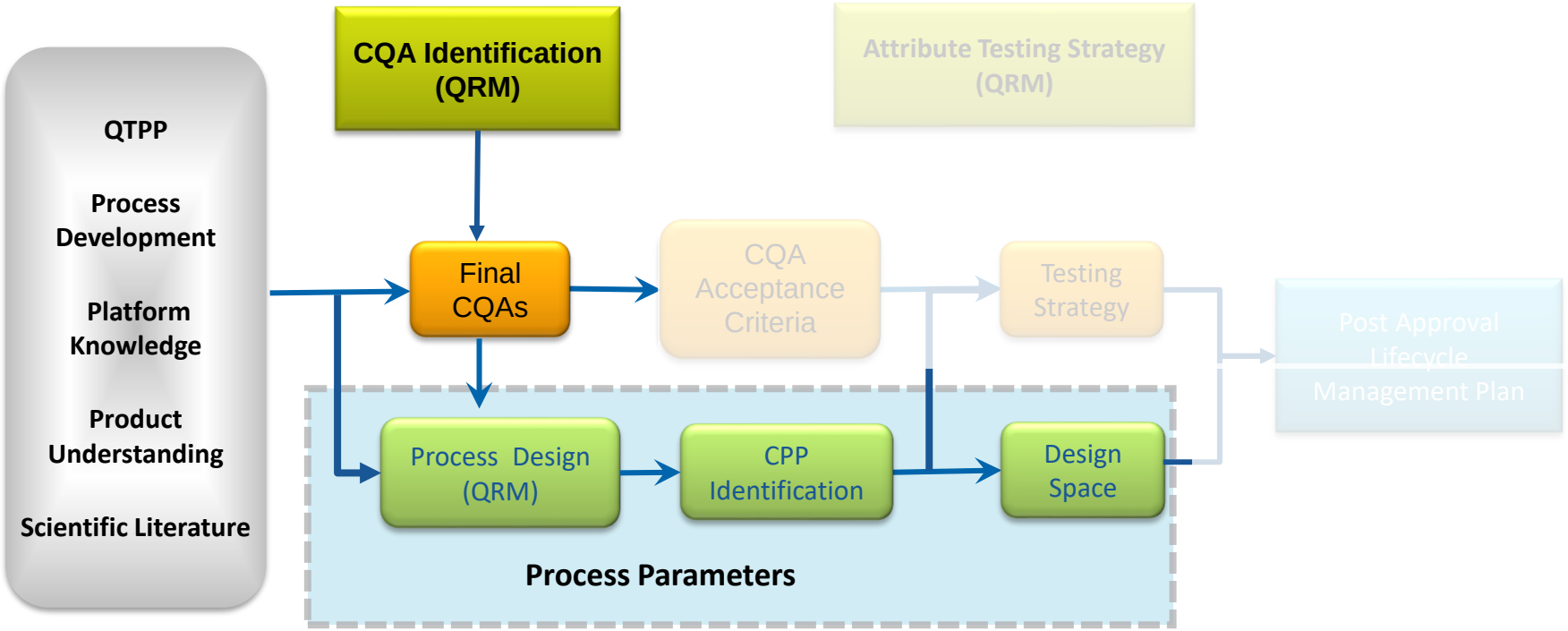
Critical Process Parameters

What attributes should be measured?

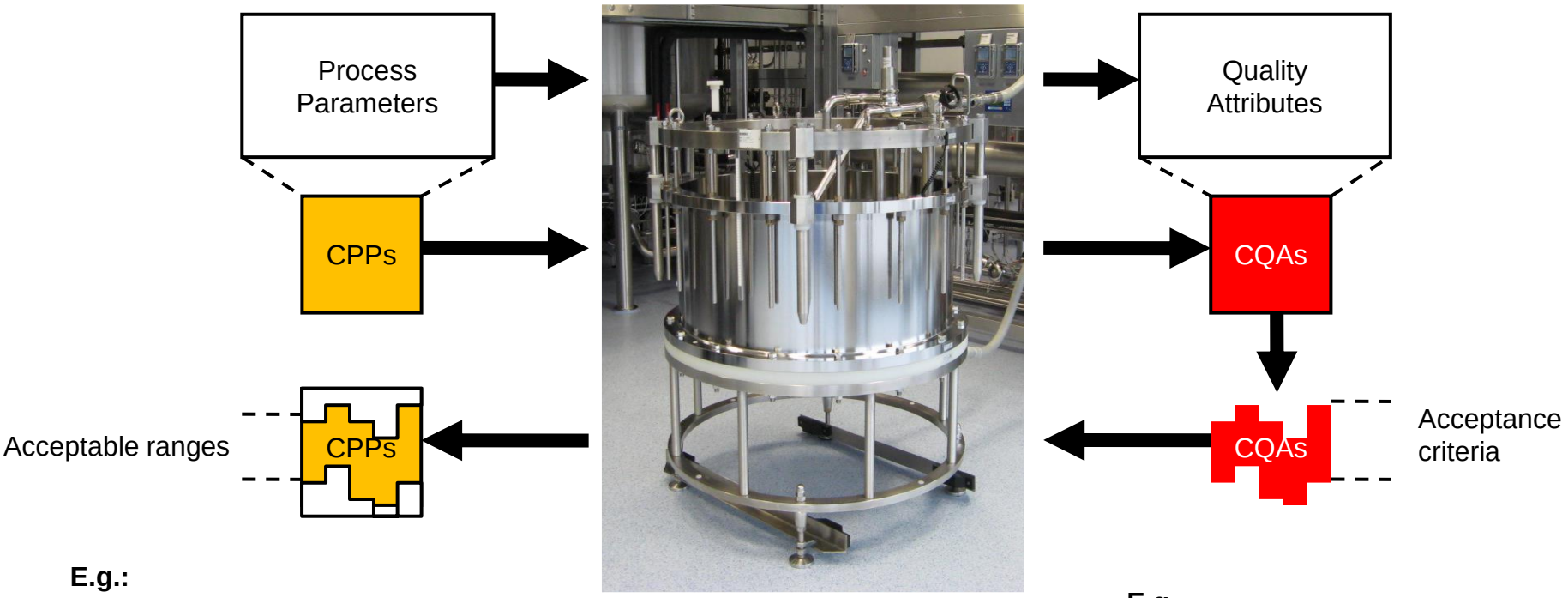


Critical Process Parameters

How do we determine Critical Process Parameters?

ICH Q8(R2): 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.



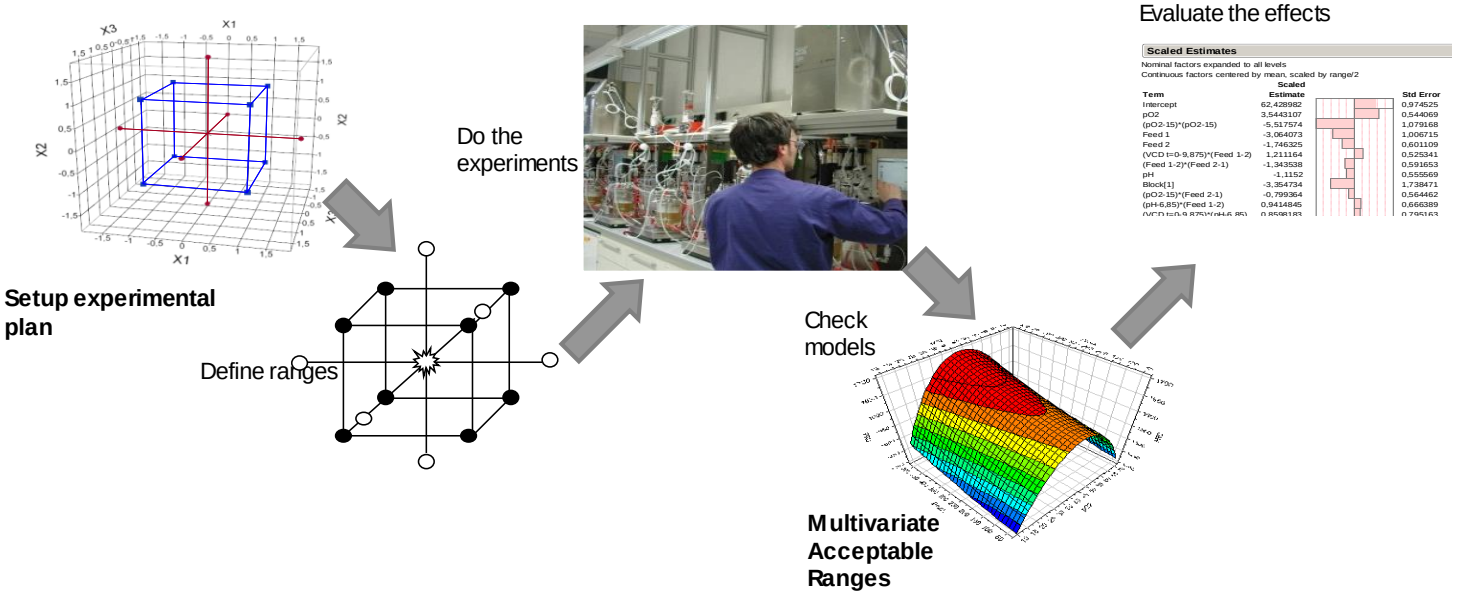
E.g.:
Temperature
pH
Culture Duration
Bed Height

E.g.:
Fragmentation
Host Cell Protein
Glycosylation

Critical Process Parameters and Design Space

How do we determine Critical Process Parameters?

1. Identify potential Critical Process Parameters via QRM
2. Process Design Studies for each process step to determine acceptable ranges and process parameters critical for a given process step



3. End-to-end (linking) Process Design Study to develop overall design space

Example

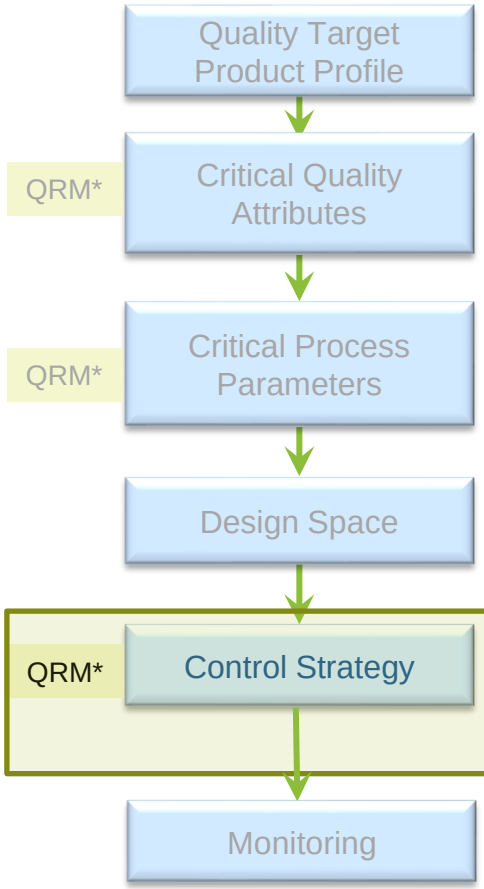
Identification of CPPs

Process Step	Process Parameter	Scale Tested	Quality Attributes Tested[a]
Freeze	Heat Transfer Fluid Temperature (or Product Temperature) Bulk Volume in Freeze/Thaw Vessel Freeze Cycle Duration Number of Freeze/Thaw Cycles	Manufacturing scale and small-scale model	Size Variants, Charge Variants, COC, Protein Concentration, Visible/Subvisible Particles, pH, Osmolality, Potency
Thaw	Heat Transfer Fluid Temperature Bulk Volume in Freeze/Thaw Vessel Bulk Recirculation Start Time Bulk Recirculation Time Bulk Recirculation Flow Rate Number of Freeze/Thaw Cycles	Manufacturing scale and small-scale model	Size Variants, Charge Variants, COC, Protein Concentration, Visible/Subvisible Particles, pH, Osmolality, Potency, Identity
Pooling/ Mixing	Mixing Time Mixing Speed Product Temperature Bulk Volume	Manufactu	
Bulk Transfer from Freeze/Thaw Tank to Mixing Tank	Transfer Pressure Transfer Temperature	Manufactu	
Bioburden Reduction Filtration	Filtration Pressure Ration of Bulk Volume to Filter Surface Area Number of Refiltrations	Manufactu small-scal	

Outcomes – CPP summary

Process Step/Parameter	Acceptable Range	Range Type	CPP Type
Freeze			
Bulk Volume in Freeze/Thaw Vessel (L)	120 L: 14 – 120 300 L: 50 – 300	MAR	Non-CPP
Heat Transfer Fluid Temperature/Product Temperature[a]			
Temperature-Feedback Approach (°C)	Heat Transfer Fluid Temperature ≤ – 43	MAR	Non-CPP
Fixed Freeze-Operation Time Approach (°C)[a]	Product Temperature is ≤ – 36°C for ≥7.5 hours	MAR	Non-CPP
Freeze Cycle Duration			
Temperature-Feedback Approach			
Duration Product Temperature ≤ – 36°C (hours)	120/300 L F/T Tank: ≥7.5	MAR	Non-CPP
Maximum Duration to Achieve Freeze Completion (hours)	≤35	MAR	Non-CPP
Fixed Freeze-Operation Time Approach			
Minimum Freeze Time (hours)	≥15	MAR	Non-CPP
Maximum Duration to Achieve Freeze Completion (hours)	≤35	MAR	Non-CPP
Number of Freeze Cycles	≤5	MAR	Non-CPP
Thaw			
Bulk Volume in Freeze/Thaw Vessel (L)	120 L: 14 – 120 300 L: 50 – 300	MAR	Non-CPP
Heat Transfer Fluid Temperature			
Temperature-Feedback Approach (°C)	23 – 26	MAR	Non-CPP
Two-Step Approach (°C)	23 – 26 (Stage 1) and 16 – 26 (Stage 2)	MAR	Non-CPP

QbD Elements – Framework Begins with the End in Mind



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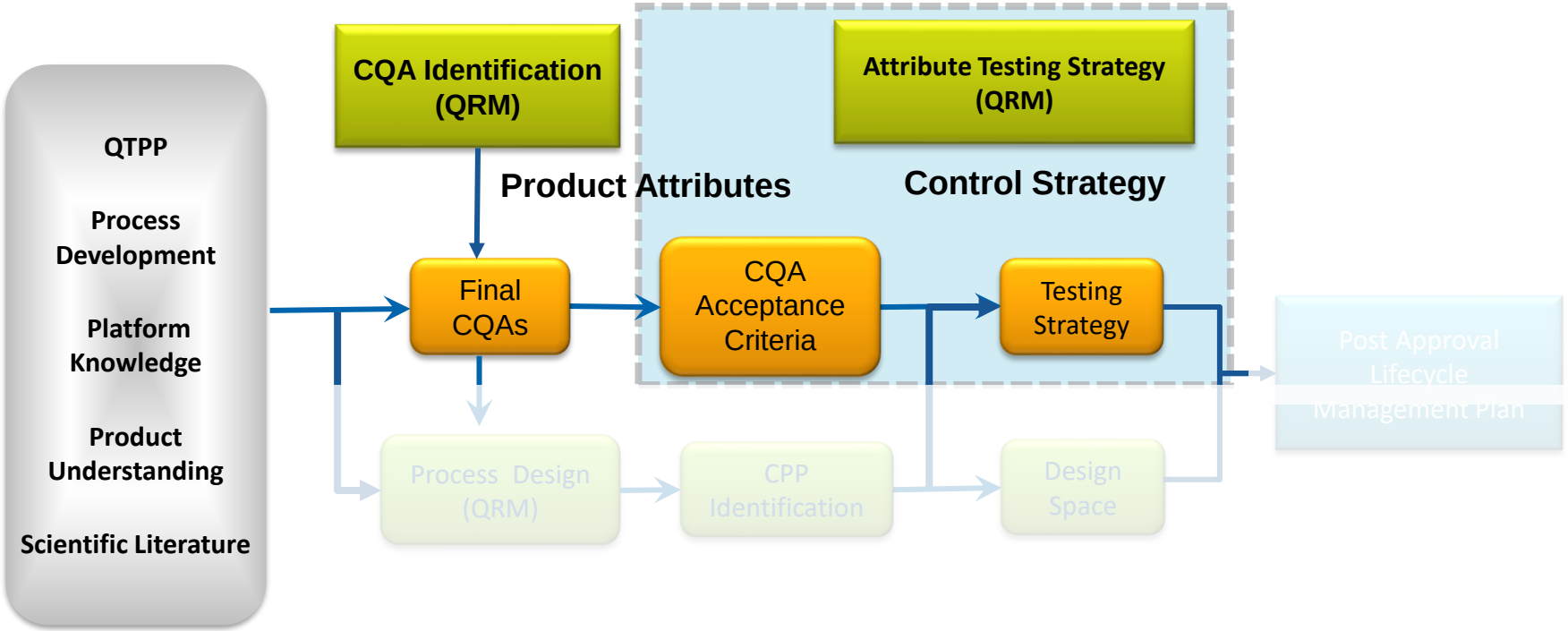
Control Strategy

Systematic Definition of the Testing Strategy

Do we have the right tests and criteria (limits)?



Quality by Design risk assessment tools integrate product and process knowledge into the Control Strategy

Critical Quality Attributes

CQA Acceptance Criteria (CQA-AC)

The CQA-AC represents a numerical limit a CQA must meet at a given unit operation in order to ensure the desired quality of the product.

- Based on patient impact and not based on product-specific (clinical) manufacturing
- Collective effect of QAs considered to ensure PK and biological activity
- Drive CPP and Design Space identification and definition of control strategy

CQA-AC are established based on:

- Product-specific non-clinical and clinical experience
- Platform knowledge and published literature
- Process capability and testing strategy considerations
- For CQAs that are not formed, no CQA-ACs are set

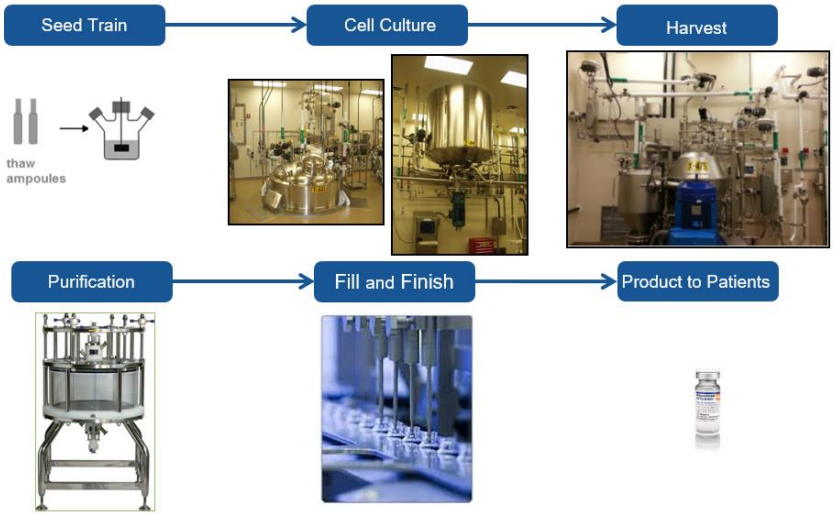
May extend beyond product-specific clinical and non-clinical historical ranges with justification

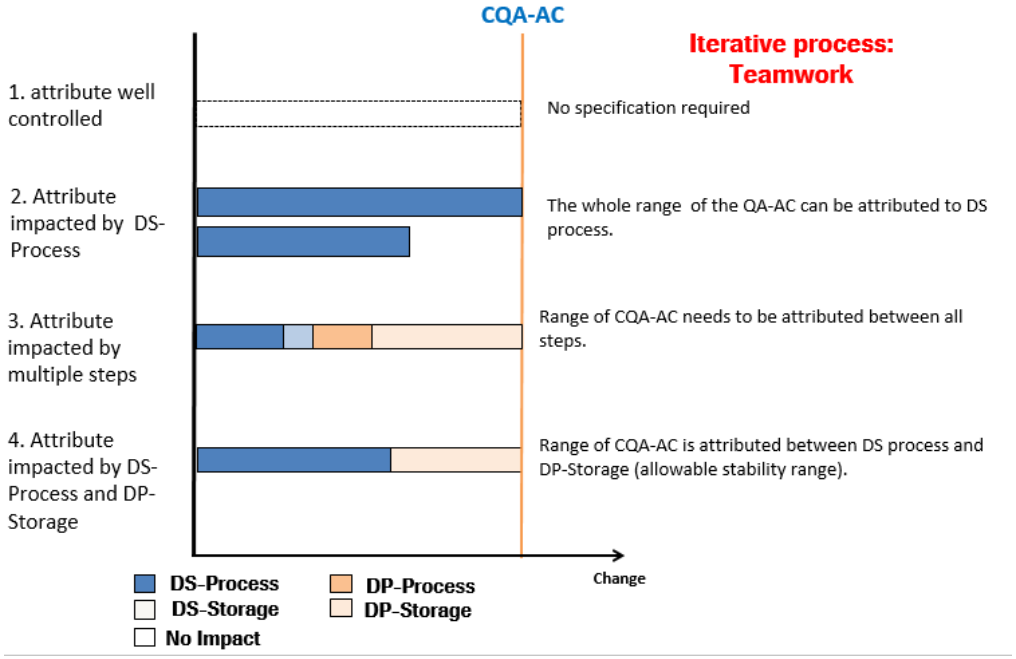
Not necessarily product release criteria

Control Strategy

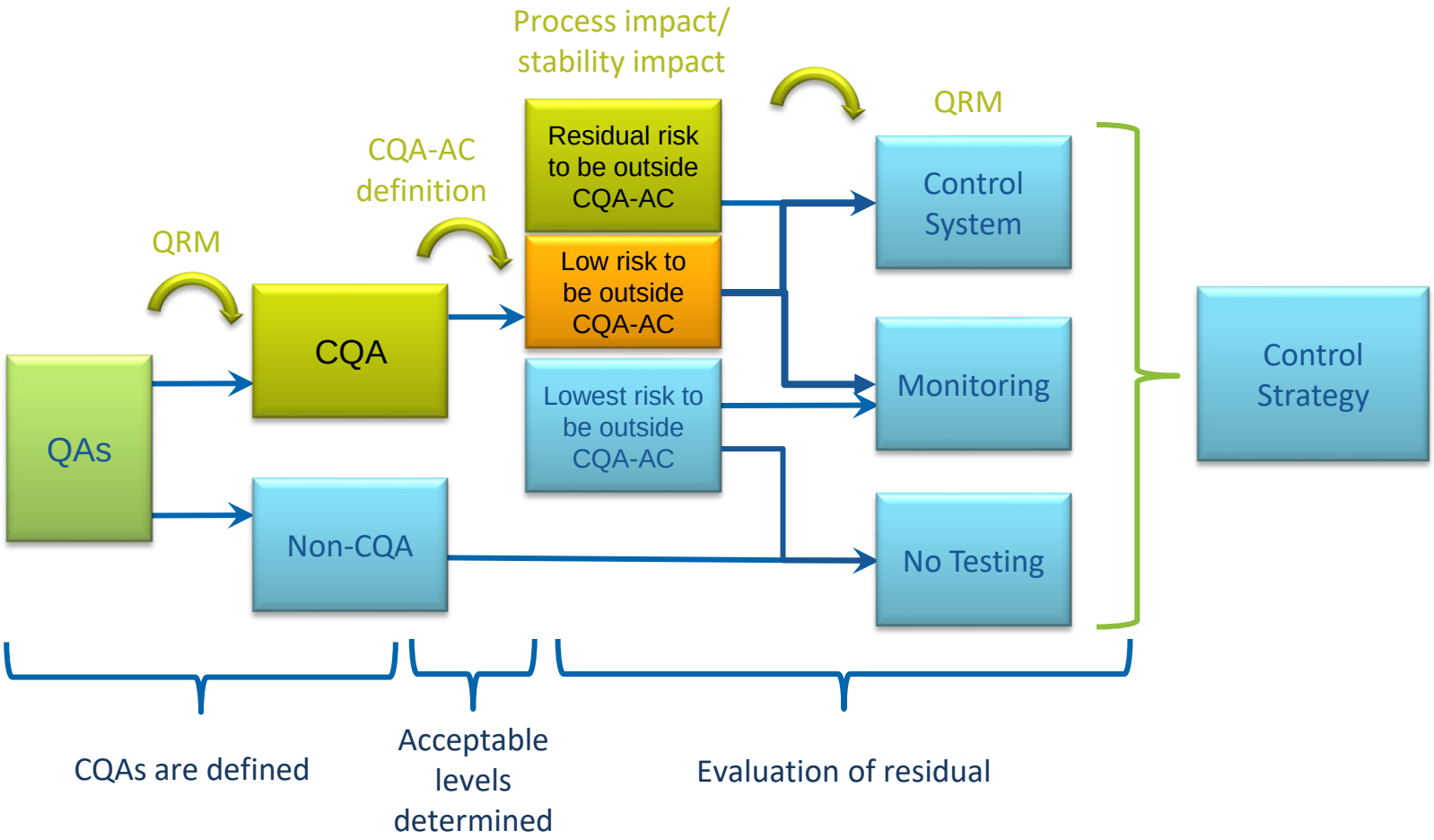
Setting of the acceptance criteria can be an iterative process

Illustrative example

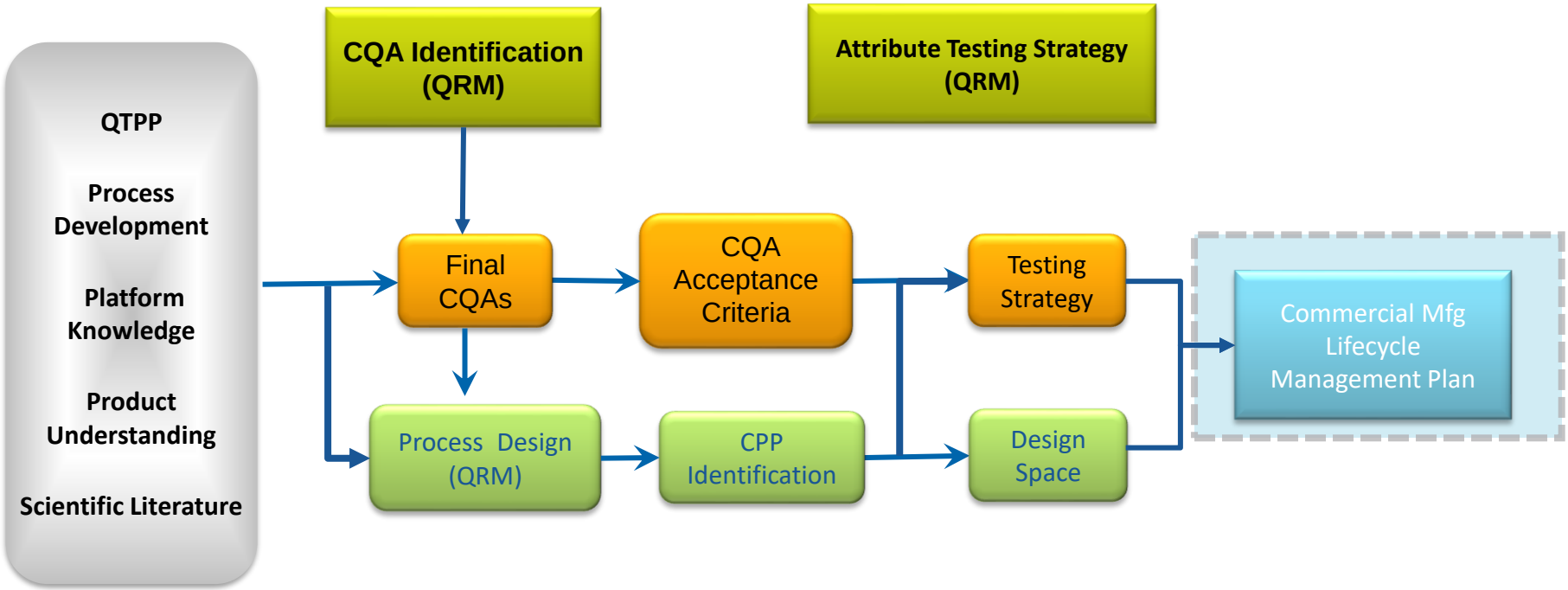




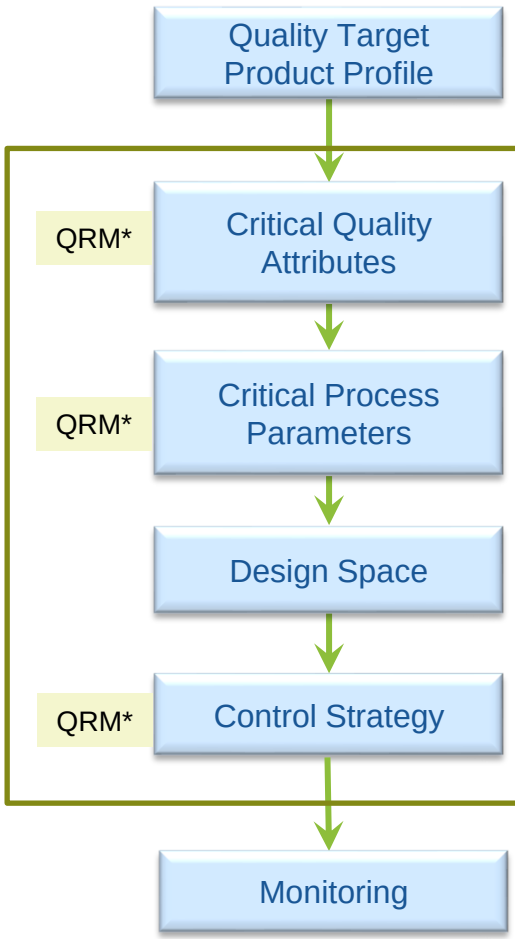
Control Strategy



Piecing Things Together



QbD Elements – Recap so Far



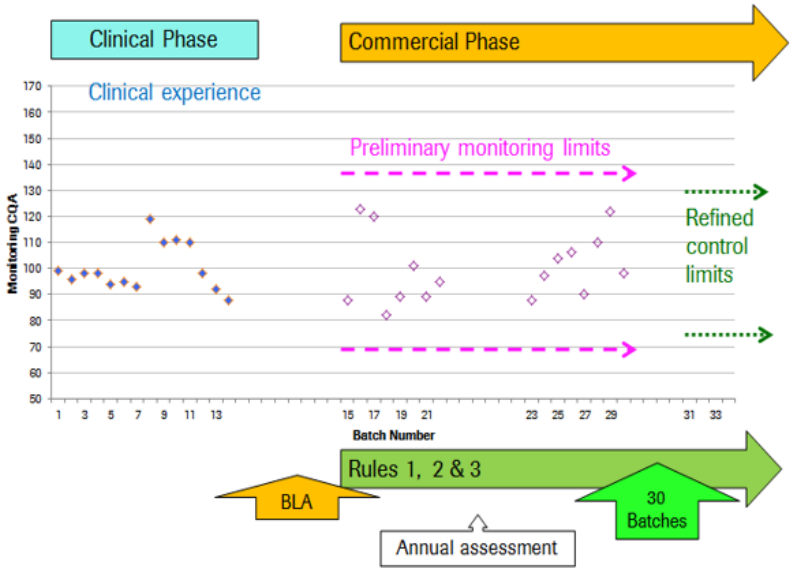
Systematic approach to development that begins with predefined objectives and emphasizes **product** and **process understanding** and **process control**, based on sound **science** and **quality risk management**.

Process development → completed prior to product approval

Commercial manufacturing lifecycle management

Typical Elements of the Commercial Manufacturing Lifecycle Management

- **Monitor** the production process and product quality attributes to ensure that both remain within a controlled state post-approval
- **Update the control strategy** as necessary based on further process and product knowledge
- **Manage changes** to process parameters within the design space



- Systematically adds to process understanding →
- Continuous improvement to enhance process overtime →
- Assure product quality to patients

Lecture Outline

Background

Quality by Design (QbD) in Biologics Manufacturing

Summary

Questions and Answers with Industry Panel

Quality by Design (QbD)

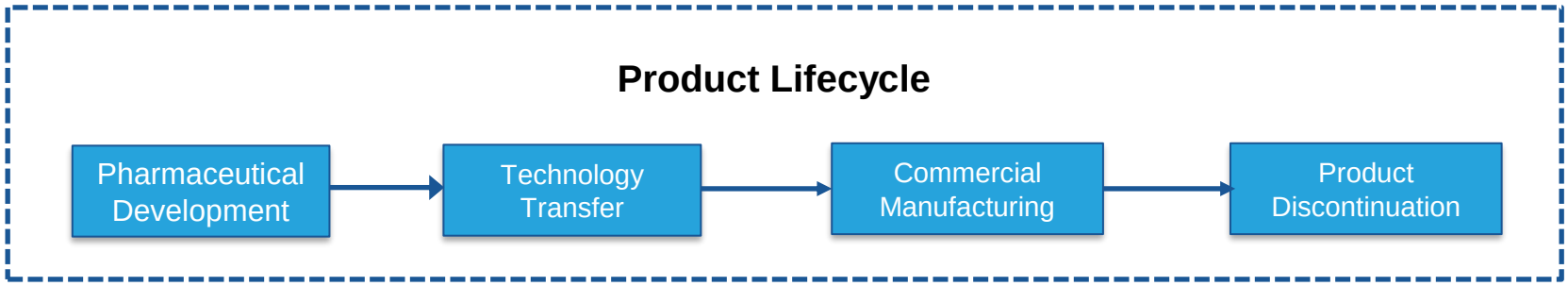
Pharmaceutical Quality System, ICH Q10

Quality by Design (ObD)

- Systematic approach applied to the development of a Product
- Emphasis on process and product understanding
- Science and risk-based approach used in the development of a product
- QbD elements are covered in ICH Q10, Pharmaceutical Quality System

ICH Q10, Pharmaceutical Quality System

Applies to systems supporting the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.

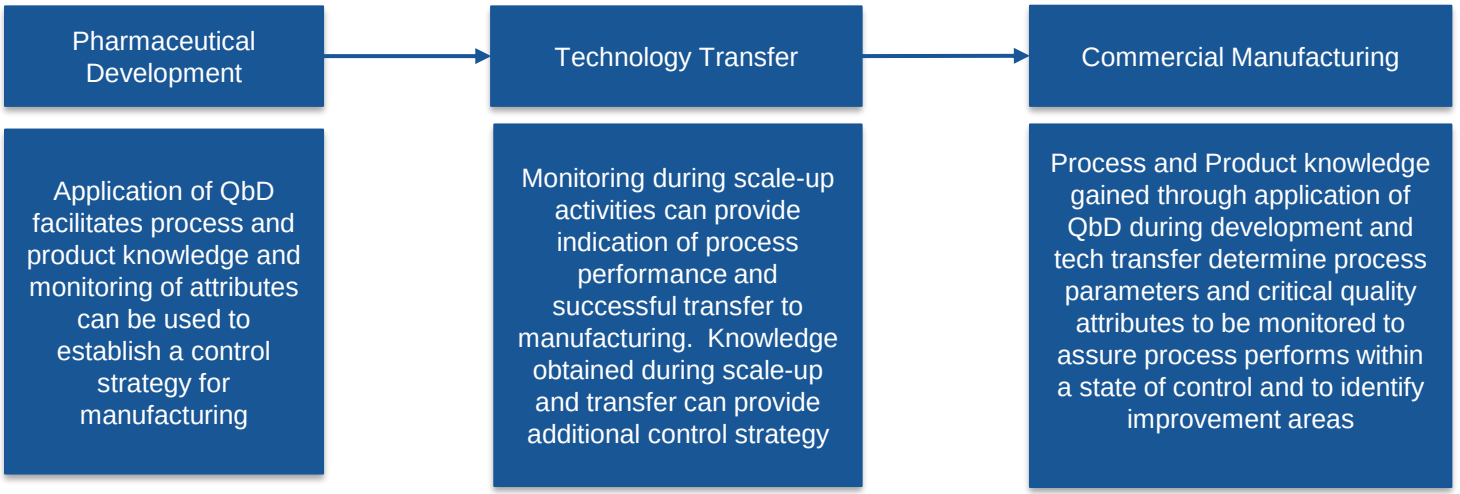


Quality by Design (QbD)

Pharmaceutical Quality System, ICH Q10

ICH Q10, Pharmaceutical Quality System

- Provides quality management throughout the lifecycle of the product
- Considers the different goals and knowledge available for each stage of product life cycle
- Encourages the use of science and risk-based approach at each lifecycle stage
- Facilitates innovation and continuous improvement to improve product quality



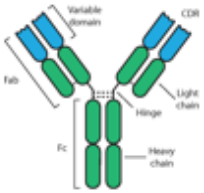
Lecture Outline

Background

Quality by Design (QbD) in Biologics Manufacturing

Summary

Questions and Answers



Workforce of the Future

UC DAVIS
UNIVERSITY OF CALIFORNIA

Q&A Panelists

Meli Gallup – Genentech – Director Global MSAT Biologics Drug Products
Rosalina Padilla – Grifols – Director Quality Assurance
Ryan Chaney – Genentech – Senior Engineer Global MSAT Drug Substance
Nassim Farrokhzad – AstraZeneca – Associate Principal Scientist Drug Product & Combination Products