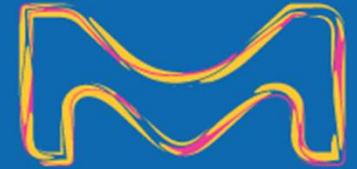


quality by design in vaccine processes

DCVMN Webinar; Feb 26, 2026

Subhasis Banerjee Ph.D
Principal Process Consultant, APAC



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Agenda

01 QbD Background & Explanation

02 QbD Application in Vaccine

03 Case Study:
QbD Application in Ultrafiltration Process



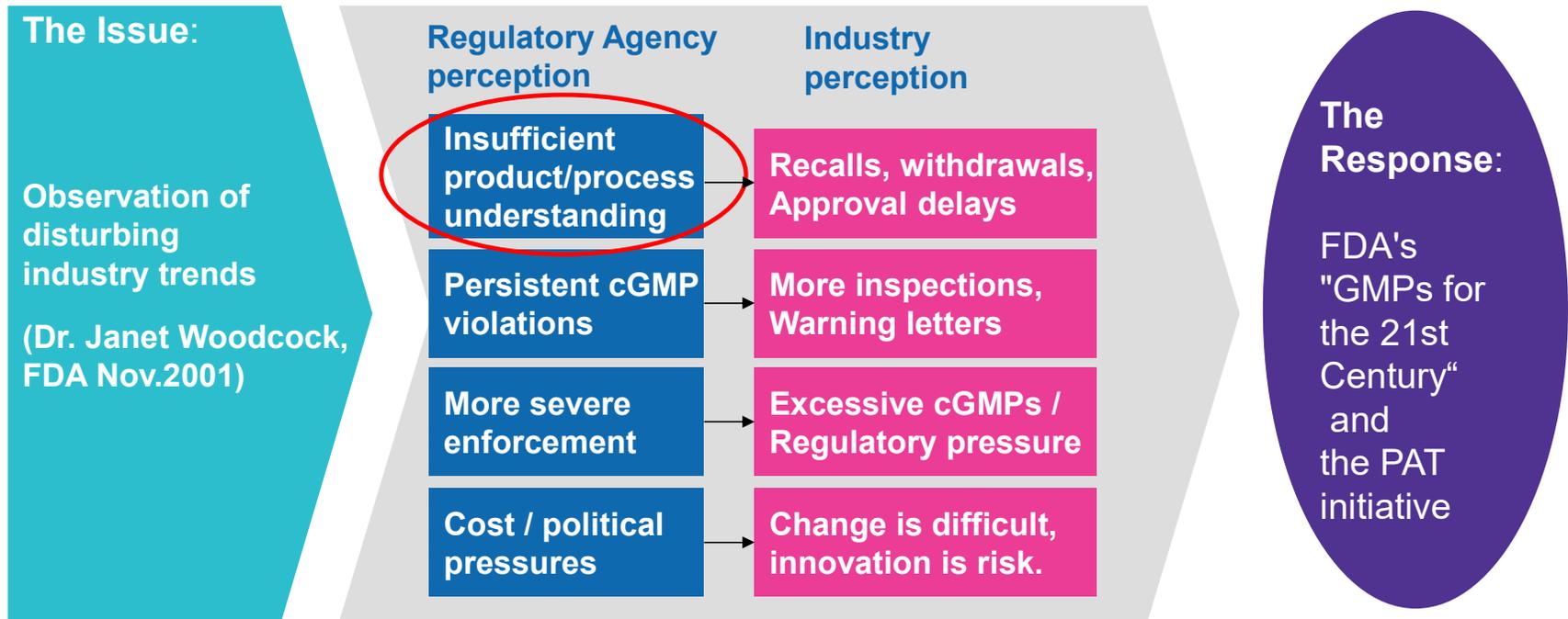
01. QBD Background

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QbD Background: Regulatory Initiative

Low industry efficiency and high regulator workload triggered initiatives



Quality by Design (QbD) related guidelines:

ICH Q8, 9, 10, 11

FDA Process validation guidance

EMA: EMA/CHMP/QWP/811210 (Parametric Release); Process validation guidance



QbD Background: Regulatory Initiative

What is QbD?

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From **test
quality**
↓
to
**Built
quality**

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 Q8R1).

"...quality cannot be tested or inspected into a finished product, but quality, safety & effectiveness must be designed and built into a product and its manufacturing process"

According to the FDA:

Designing and **developing manufacturing process during the product development stage** to endure a **predefined quality** at the **end of manufacturing process**



QbD Background: Regulatory Initiative

Quality is the Key

Suitability of either a drug substance or product for its intended use

(ICH Q6A)

Efficacy/Strength	Does the production process result in product/residues that interfere with final product strength or efficacy?
Identity & Purity	Does the production process result in product/residues that interfere with final product purity?
Safety	Does the production process result in product/residues that are toxic to the patient?



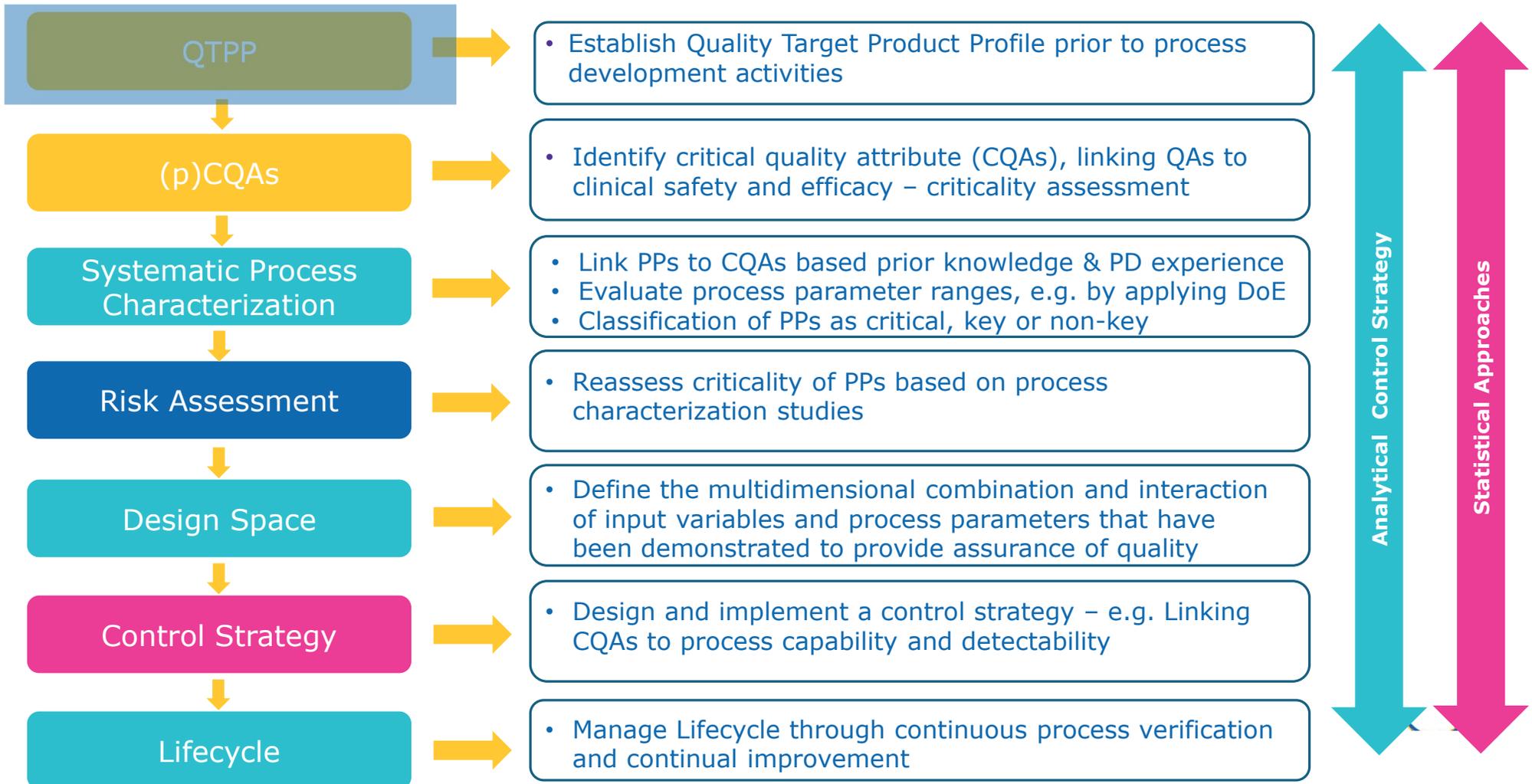
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02. QBD Application in biopharmaceuticals



QbD Framework Beginning with the end in mind

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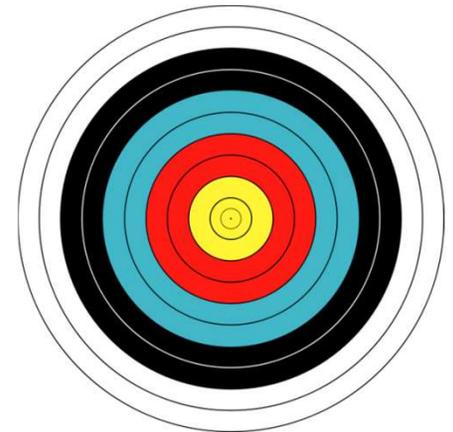


QbD Framework Quality Target Product Profile (QTPP)

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QTPP is defined as 'prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized.' (ICH Q8 (R2))

- Route of administration and intended use (in a clinical setting or at home)
- Dosage form, delivery system
- Dosage strength
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the
- Drug Product dosage form being developed
- Drug Product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product



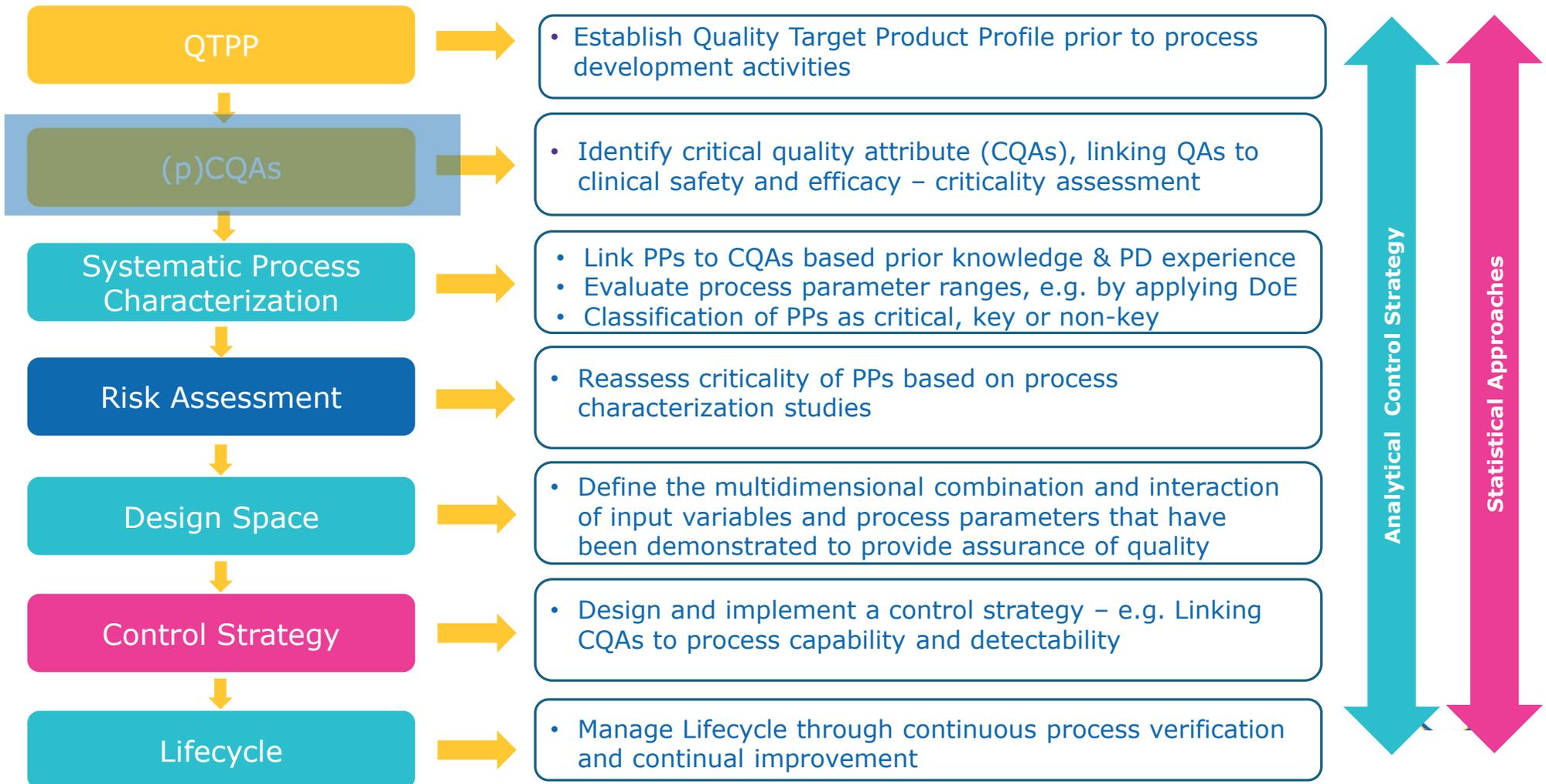
Quality Target Product Profile (QTPP)-An example of Vaccine QTPP

<p>Key claims</p>	<ul style="list-style-type: none"> • Easy to administer, 0.5 mL subcutaneous delivery in an outpatient healthcare setting using a 1 mL syringe (27G ½-inch needle). • Stability: Two years at room-temperature storage, Four years at 2–8 °C, and 24 hours’ physical and chemical stability following reconstitution at 2–8 °C, or eight hours at room temperature (achieves WHO stability requirements) • No animal- or human-derived products are used in the manufacture of A-VAX. • Sterile product: the drug substance (Ps-VLP) can be sterile filtered.
<p>Formulation and dosing</p>	<ul style="list-style-type: none"> • Three doses (containing 5 mcg each of Ps 1–4 and 50 mcg Ps 5; adsorbed to 300 mdg aluminum adjuvant as Ps-VLPs) administered two months apart (preferably zero-, two-, and four-month pediatric vaccine schedule) • Lyophilized and reconstituted with standard diluents containing adjuvant: rapid reconstitution profile with viscosity of 1–3 cP.\Composition: sugar, surfactant, buffer (isotonic pH), and Ps-VLP conjugate. • Label volume 0.5 mL filled (actual fill volume is greater than the label volume to account for loss). • Single-dose vial (ISO2R vial, clear, Type 1 glass), latex-free stopper (13 mm coated stopper), and seal (13 mm aluminum seal with flip off plastic button) • Secondary packaging and shipping: allowed shipping-excursion temperature: 2–40 °C for three days in a carton (ten vials per carton).



QbD Framework Beginning with the end in mind

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QbD Framework CQA Determination

- Risk Assessment as a tool
- Based on safety/potency
- Evaluation of impact and its uncertainty
- Higher score for efficacy or safety used
 - Efficacy considers effects biological activity, PK and PD

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Critical

		Uncertainty		
		1 (Low)	2 (Medium)	3 (High)
Severity	10 (High)	10 (Critical)	20 (Critical)	30 (Critical)
	3 (Medium)	3 (Potential)	6 (Potential)	9 (Potential)
	1 (Low)	1 (Non-critical)	2 (Non-critical)	3 (Potential)

Non-Critical

Potential-Critical

Value	Severity	Severity of Effect
1	Low	Variability in attribute has minor or negligible potential for decreased safety/efficacy. Negligible or minor transient adverse effects are expected based on historical experience.
3	Medium	Variability in attribute may have moderate potential for decreased safety or efficacy within the clinical history of the product. Attribute may result in manageable adverse effect seen historically but no new adverse effects.
10	High	Variability in attribute may have potential for severe effect on patient. Potential significant change in safety/efficacy or risk/benefit profiles. May result in a serious (reversible or irreversible) adverse effect.

Value	Severity	Prior Knowledge	Pre-Clinical Studies	Clinical Studies
1	Low	Well characterized effect based on extensive data (<i>in vitro</i> , <i>in vivo</i> , or clinical). Large body of knowledge in the literature.	Demonstrated relevance of animal model results. Extensive <i>in vitro</i> and <i>in vivo</i> studies for this product.	Significant clinical experience with this product.
2	Medium	External published literature available. Well characterized effect known. Internal data (<i>in vitro</i> , <i>in vivo</i> , or clinical) from this or similar class products.	Only moderate <i>in vitro</i> and/or <i>in vivo</i> data available for this product.	Only limited clinical experience with this product.
3	High	Limited or no published external scientific literature and no internal data from this or similar class products.	No data available for this product.	No data available for this product.

Reference: Project A Gene Case Study, 2021 ([ALL-PROJECT-A-GENE-V6-FINAL.pdf \(alliancerm.org\)](#))



QbD Background: Key Concepts Critical Quality Attribute (CQA)

Example of A-Vax

Quality/Product Attribute	Method	I*	U*	S*
Potency				
Serotypes 1-4 (correlation)	mAb-based Competitive ELISA (adsorbed)	25	2	50
Animal Model for Type 5	Murine Serology (adsorbed)	25	2	50
Purity (desorbed Ps-VLP)				
Peptidoglycan Level	Calculated	8	3	24
Monomer	Reducing CGE	25	2	50
Complexes/Aggregates	Non-reducing CGE	25	2	50
Product-derived Impurity (desorbed Ps-VLP)				
Complexes/Aggregates	Non-reducing CGE	25	3	75
Process-derived Impurity				
Activation and Conjugation Reactants	Calculated	8	5	40
Structure/Function (Charac.) (adsorbed Ps-VLP unless indicated)				
VLP Structure	Cryo-TEM	8	5	40
Ps/VLP/Adjuvant Ratio	Calculated	8	5	40
VLP Linear and Conformational Epitopes	mAb-based ELISA (desorbed)	8	5	40
Ps Size Distribution	HPSEC-MALLS-RI	25	5	125
Size of Aggregates	DLS (desorbed)	25	5	125
Extent of Conjugation (as Ps-VLP, free Ps, and free VLP)	Reducing CGE	25	3	75
Other				
Quantity (as Protein Content)	Calculated	25	2	50
Quantity (as Ps Content)	Calculated	25	2	50
Fill Volume in Container	Compendial	25	1	25
Endotoxin	Compendial	25	1	25
Completeness of Adsorption (Adsorption to Al)	mAb-based ELISA (adsorbed)	25	5	125
Aluminum Content	ICP or AA	25	1	25

CQA is defined as 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 (ICH Q8(R2)).

Key Process Attributes (KPA): Yield, COG's, process time, footprint, robustness, expandability, capital cost concerns of interest to mfrs., but not part of QbD filing

Reference: QbD for A VAX, 2012



Quality is the Key

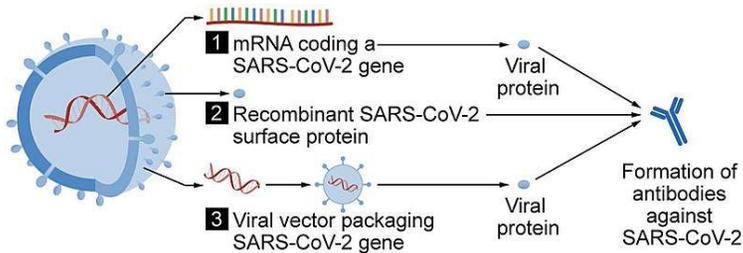
The linkage between QTPP, CQAs and CPPs is of key importance



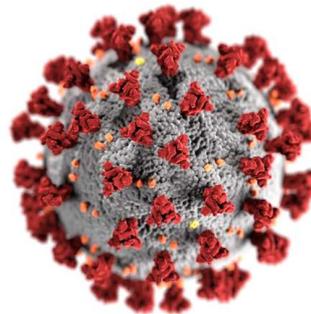
QTPP: What is the drug and what must it do to be safe, effective, (convenient)?

CQA: a Quality Attribute which, when outside a controlled range, induces a change of efficacy and/or safety

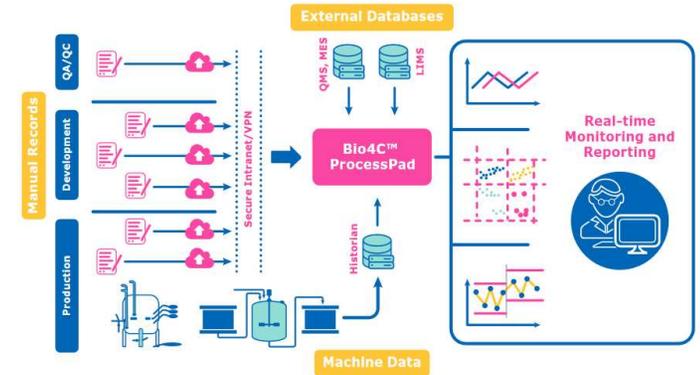
CPP: a Process Parameter which, when set outside of the Design Space, induces a change of a Critical Quality Attribute outside of its acceptable range



Source: GAO. | GAO-20-583SP



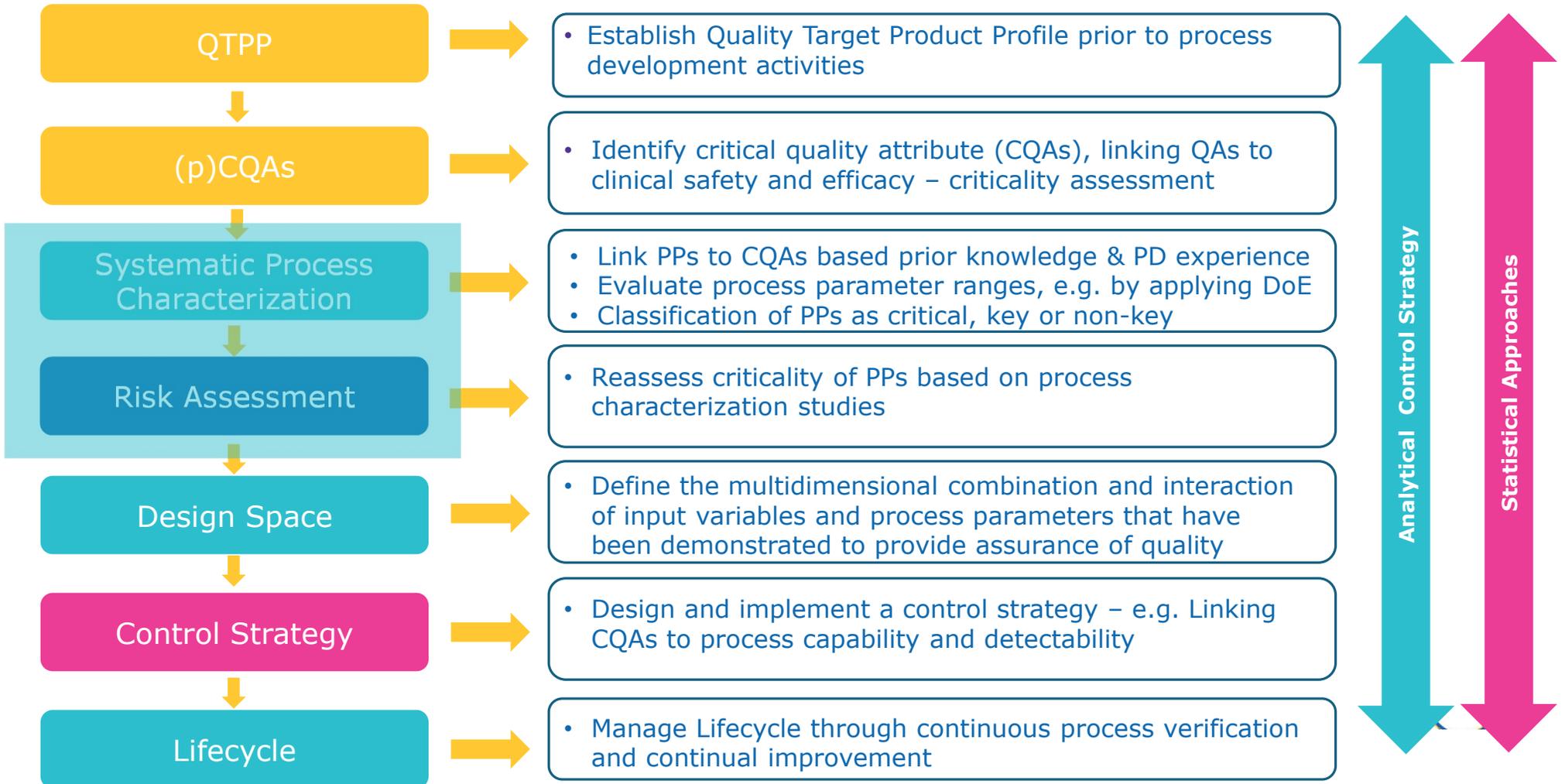
Public Domain, File:SARS-CoV-2-CDC-23312.png - Wikimedia Commons



Public Domain, File:Vaccine candidate mechanisms for SARS-CoV-2 (49948301838).jpg - Wikimedia Commons

QbD Framework Beginning with the end in mind

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Vaccine Process Understanding

Improvements towards effective, safe, and affordable vaccine

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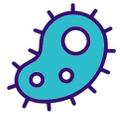
« One bug – one drug »

« One platform – multiple vaccines »

Traditional vaccine

Modern to cutting edge vaccine

Whole bacteria



Vaccines compose of inactivated bacteria

1921

Toxoid



Vaccines compose of inactivated toxin

1924

Inactivated virus



Vaccines compose of dead virus

1945

Live attenuated virus



Vaccines compose of weakened virus

1955

Recombinant protein



Vaccines with protein or protein fragment of the pathogen, assembled to closely resemble viruses

1986 - 2006

Virus-like particles



Vaccines with protein or a protein fragment of the pathogen, with a structure closely resemble the pathogen

1986 - 1991

Conjugated vaccine



Vaccines compose of sugars that mimic bacteria pathogen on a carrier protein that increase immune response

1987 - 1991

Viral vector vaccine



Vaccines that use a virus to deliver snippets of pathogen genes into human cells

2019

RNA vaccines



Vaccines compose of snippets of pathogen genes

2020

DNA vaccines



Vaccines compose of snippets of pathogen genes

2021

Various expression systems

Replication incompetent

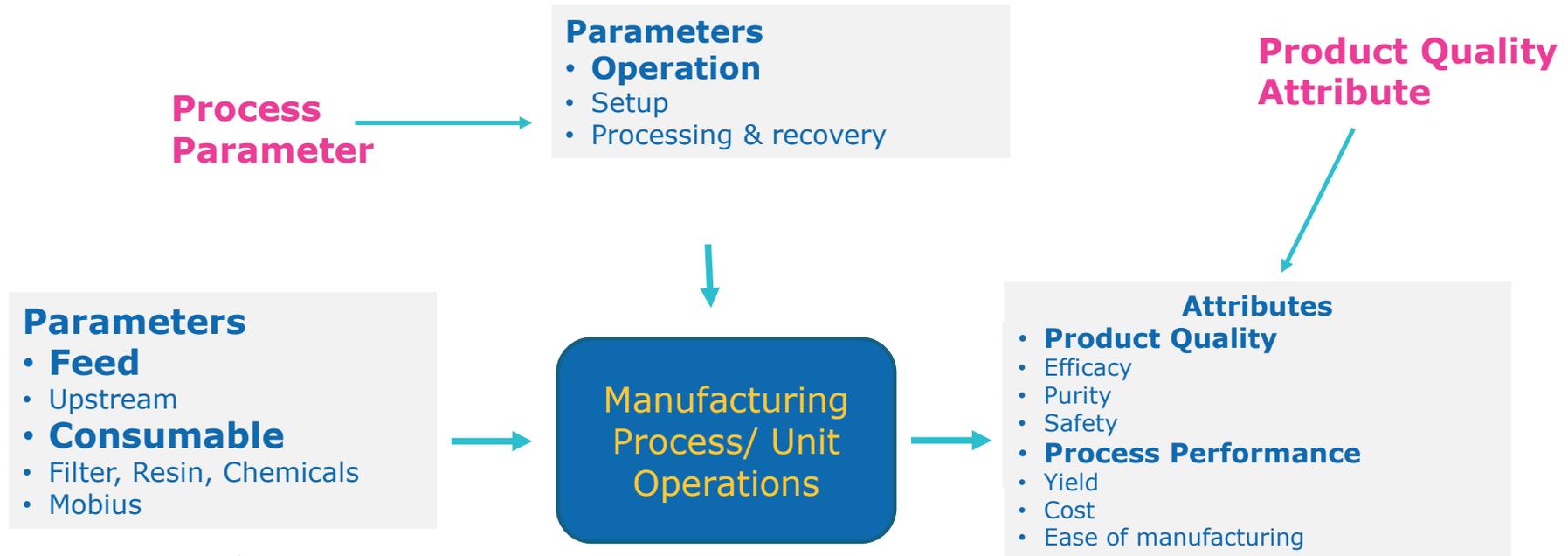
Replication competent

Synthetic mRNA

Self-amplifying (saRNA)

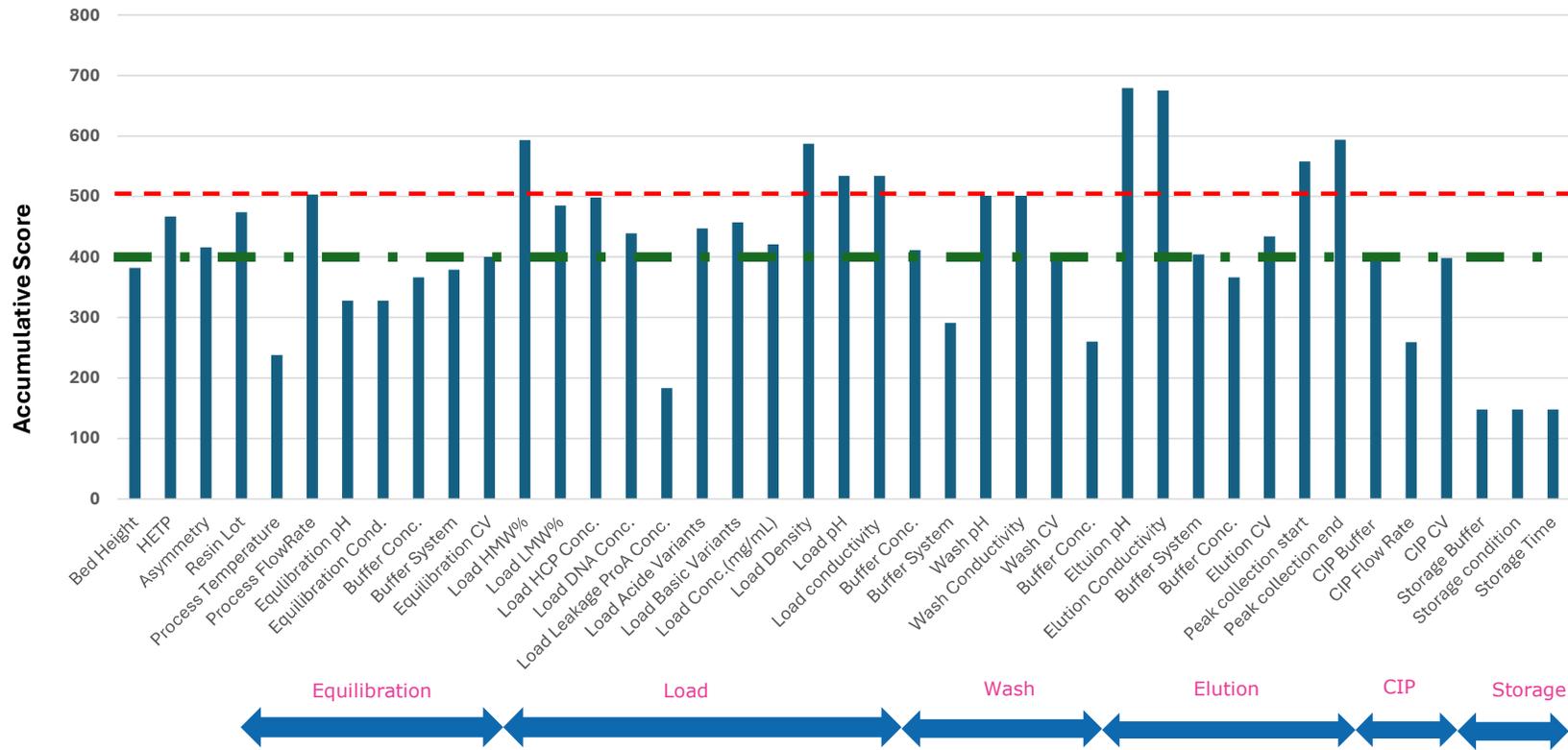


Process Characterization Key Concept



Process Risk Assessment

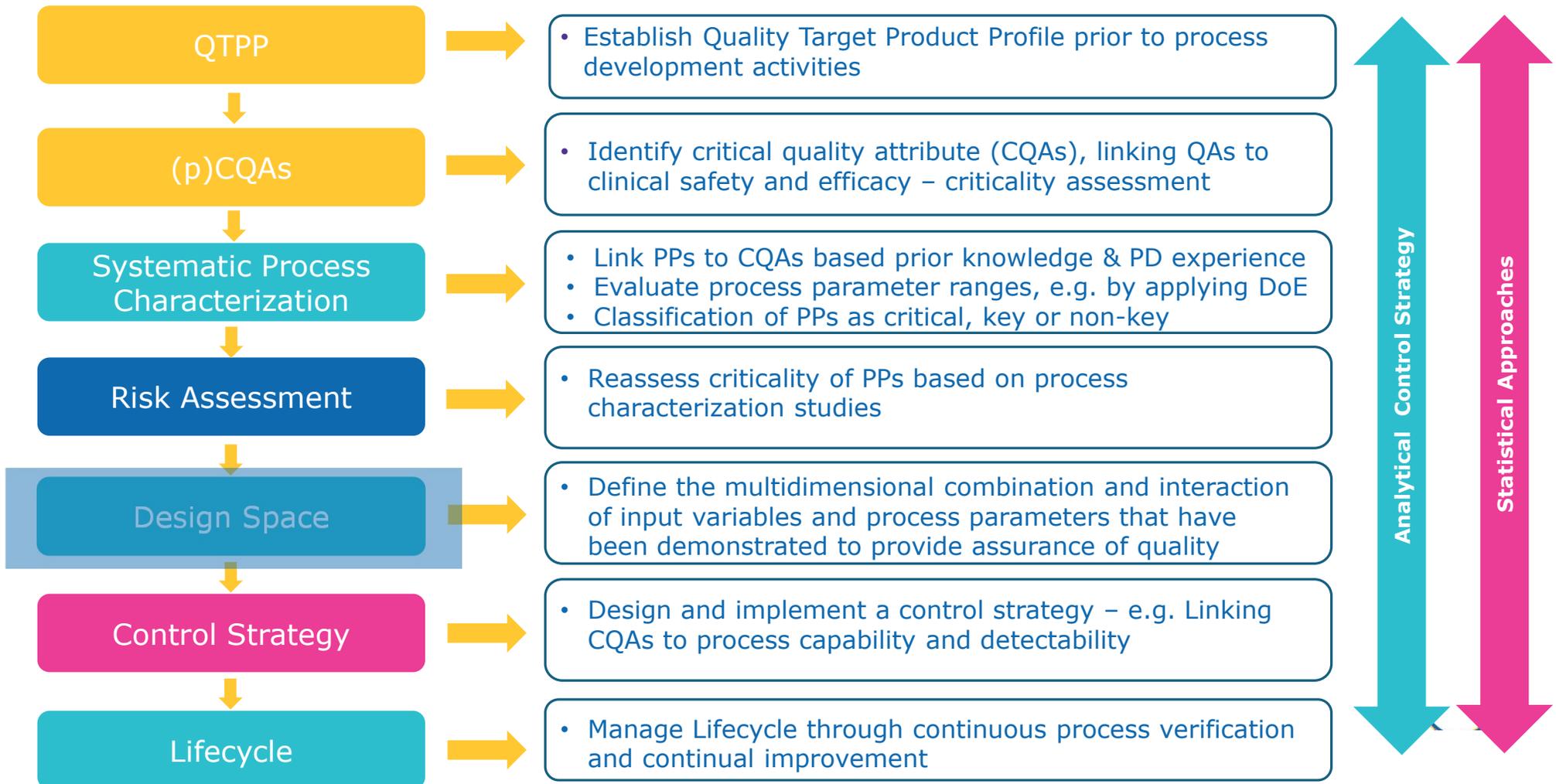
IEX Example



QbD Framework

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Design Space

How to Establish Design Space?

- **Prior knowledge**
 - Use internal knowledge from development and manufacturing to understand variables and their impact
 - Utilize external knowledge from scientific and technical publications
- **Quality Risk Management (QRM)**
 - Perform initial risk assessment of manufacturing process relative to CQAs
 - Identify the high risk manufacturing steps Failure Modes and Effects Analysis (FMEA)
- **Design of experiments (DoE)**
 - Conduct Design of Experiments (DoE) and evaluate experimental data
 - Conduct additional experiments/analyses as needed

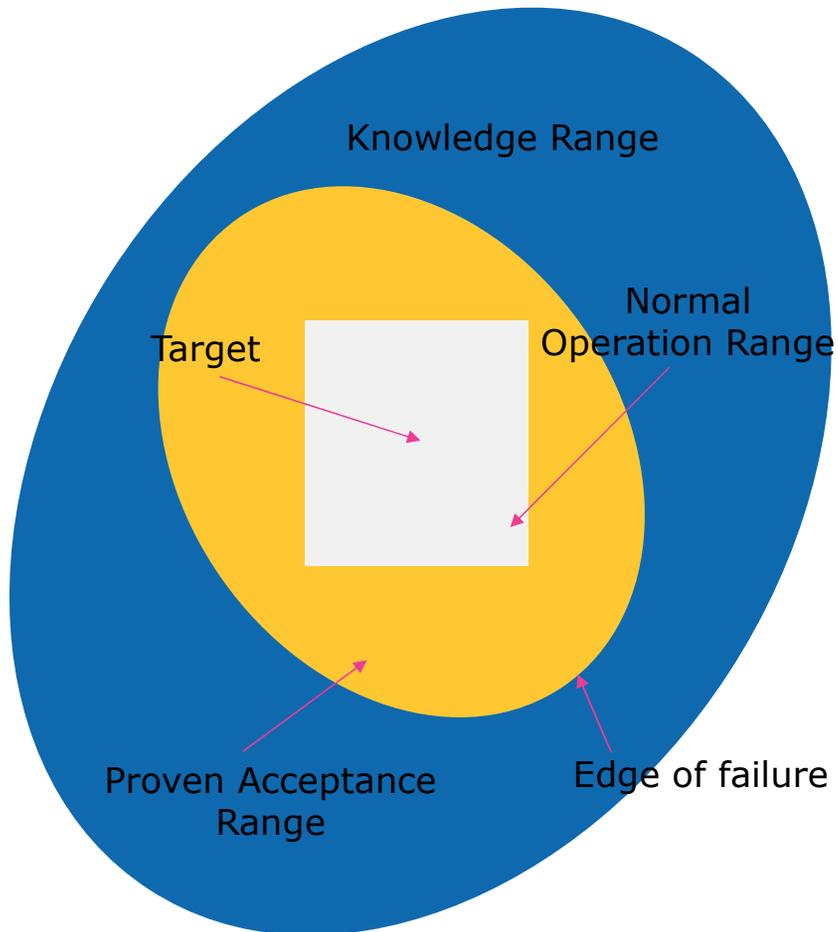
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Design Space

How to Present Design Space?

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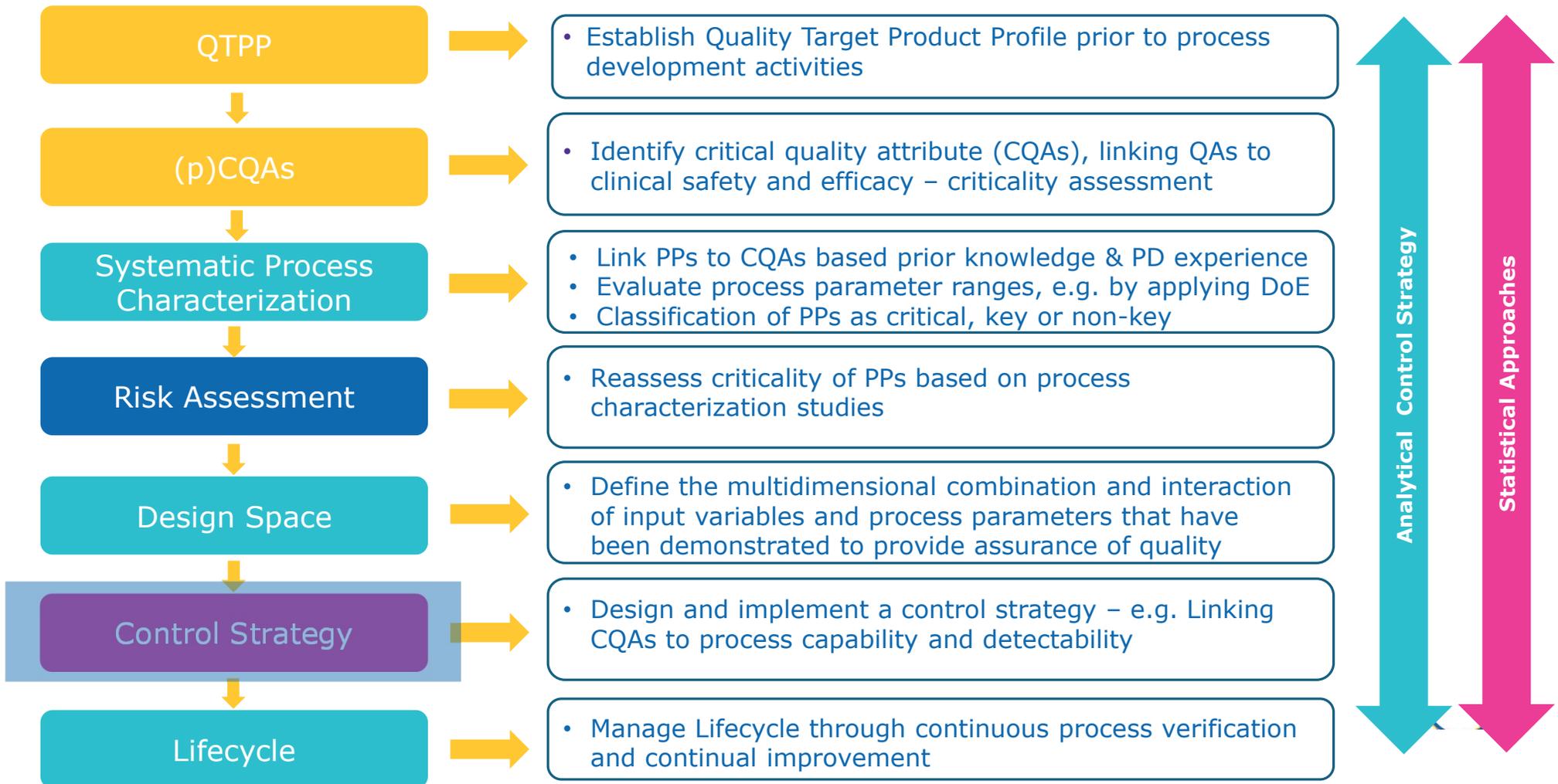
- In ideal situation, all design space, including points of failure, with an model-based equation will be presented. However, this is **not a must**.
- As an alternative, design space can be presented as ranges the green rectangle by using ranges, which is more **simple** and straight forward.



QbD Framework

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QbD Framework Control Strategy

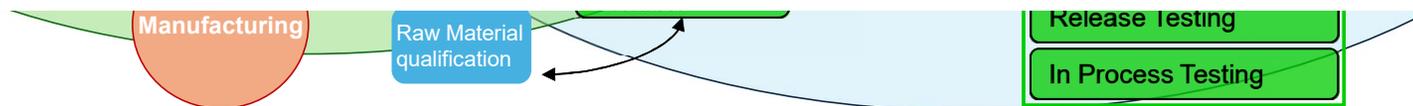
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Control Strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. (ICH Q10).

Product knowledge

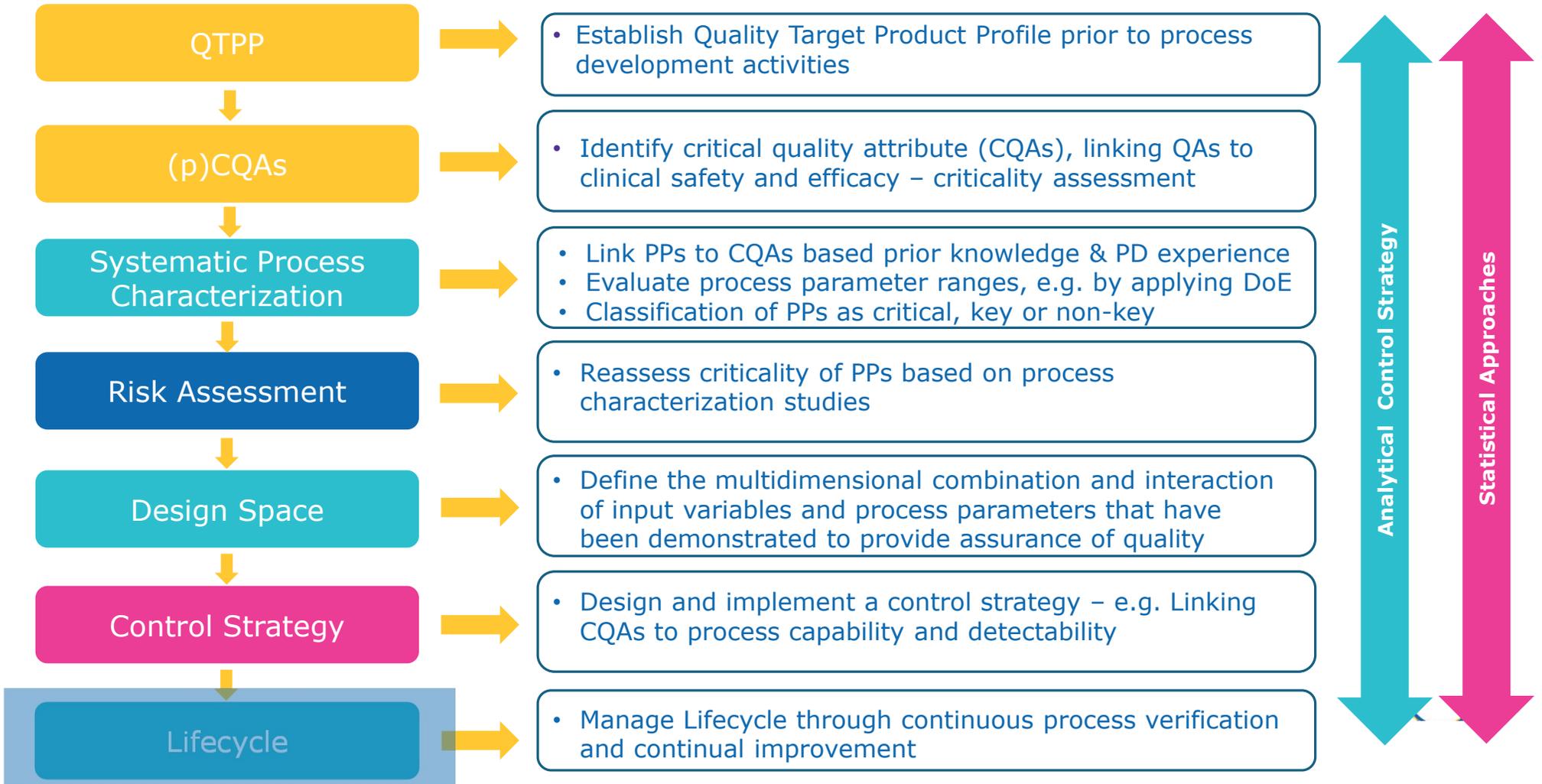
Operating Parameter	Acceptable Range	Classification	Rationale	Control strategy
Surfactant concentration	2.76-2.96	CPP	Triton X-100 concentrations <2.76% (w/v) may result in insufficient clearance	Batch record procedure
Time	60-180 min	PP	Longer times lead to aggregation, shorter times may result in incomplete inactivation	Batch record procedure
A-Gene concentration	$\leq 1 \times 10^{11}$ vg/mL	MP	No effect seen on stability or inactivation	Batch record procedure
Temperature	35°C to 40°C	PP	Higher temperatures may result in capsid instability, greater aggregation, and changes to the purity	Temperature control

Reference: Project A Gene Case Study, 2021 ([ALL-PROJECT-A-GENE-V6-FINAL.pdf](#) ([alliancerm.org](#)))

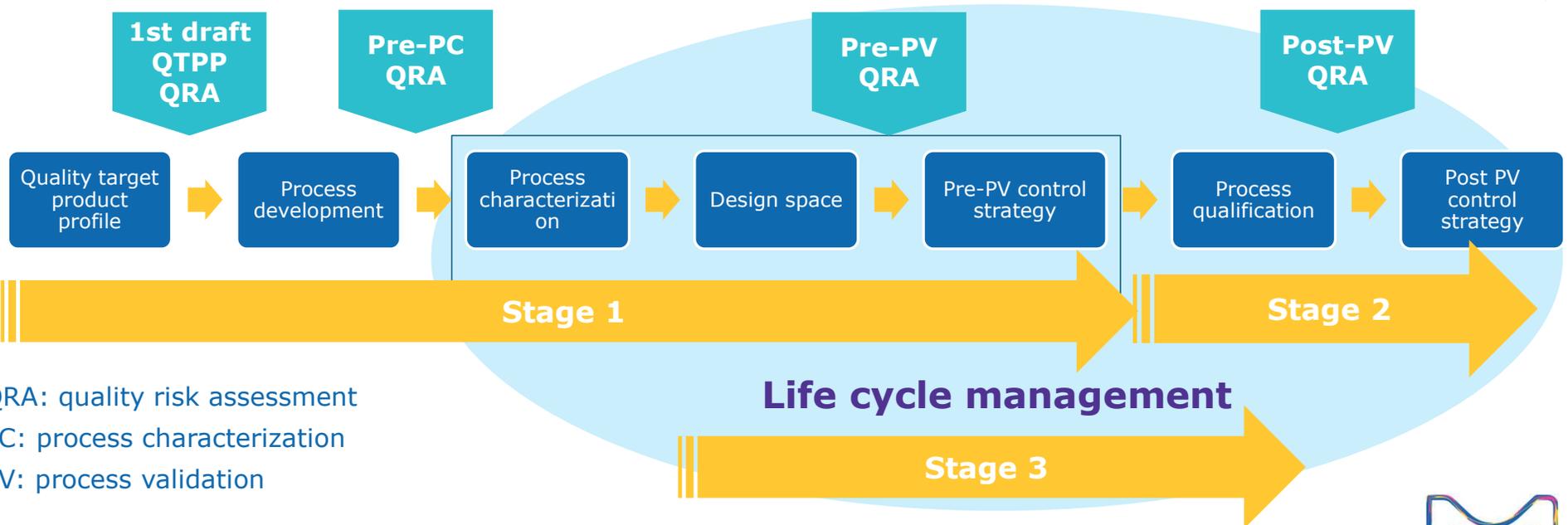


QbD Framework Beginning with the end in mind

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Process Consistency and Product Quality Along Product Life Cycle



QRA: quality risk assessment
PC: process characterization
PV: process validation

Adapted from Parenteral Drug Association Technical report 60 Process Validation: A Lifecycle Approach



03. case study: obd Application in ultrafiltration process



Basic UF Applications & Schematic

- **Clarification**

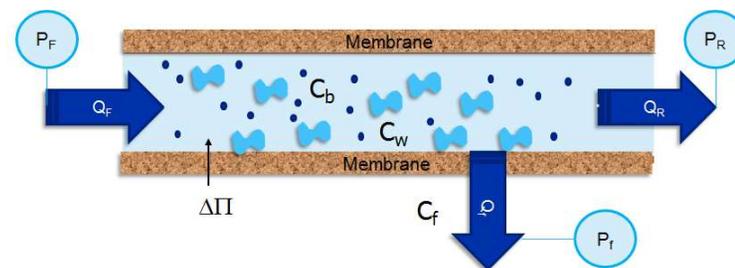
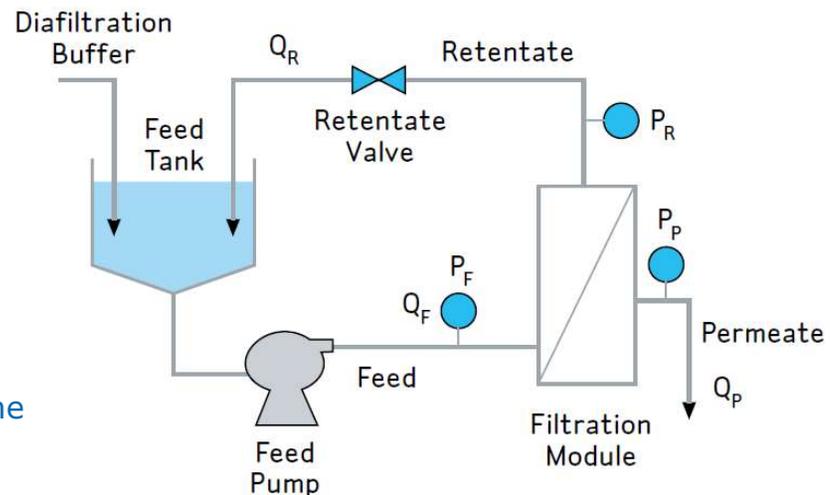
- Product passes through the membrane
- Larger particles / molecules retained by membrane

- **Concentration**

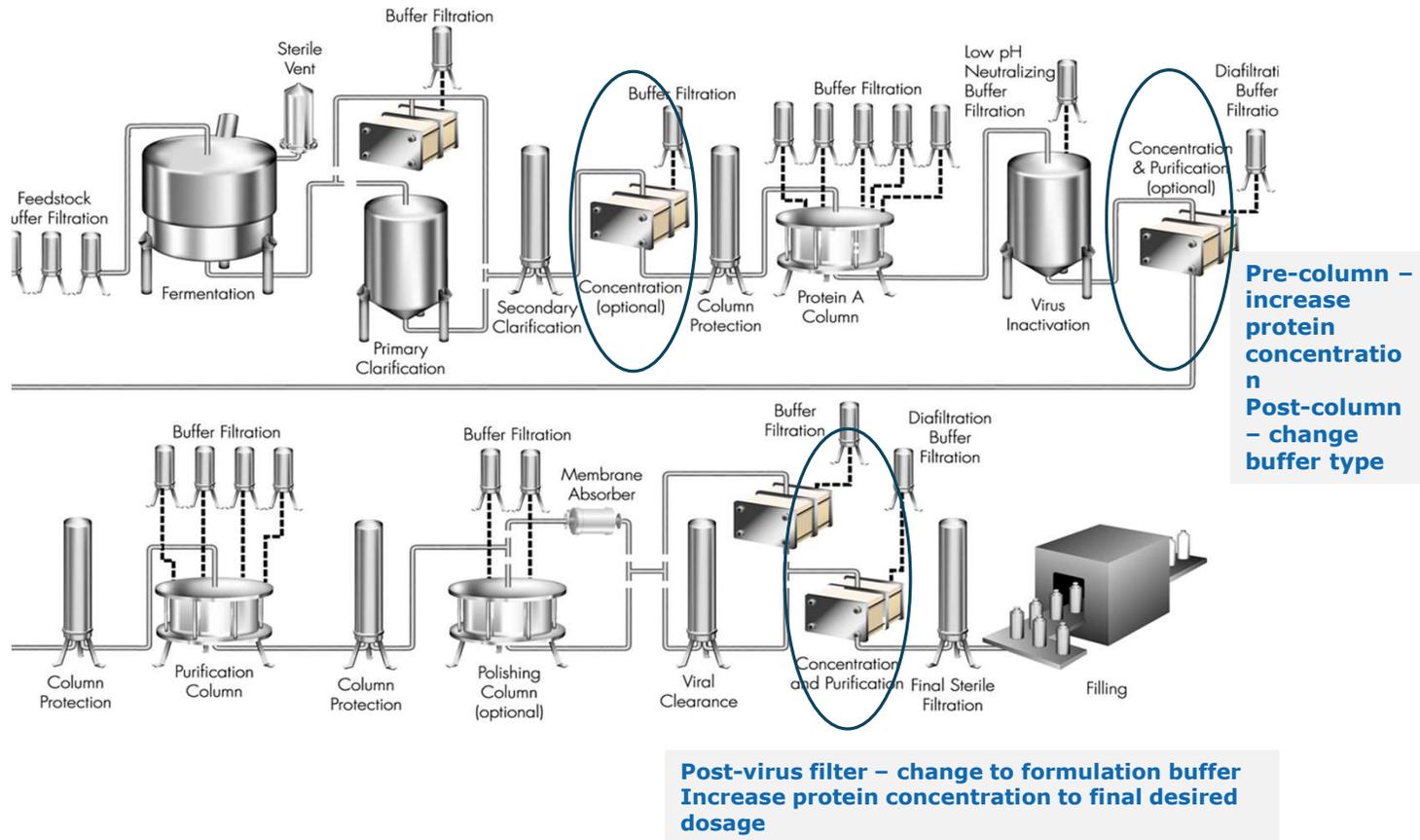
- Product retained by the membrane
- Solvent (buffer) passes through the membrane

- **Diafiltration (Buffer Exchange)**

- Product retained by the membrane
- Solvent (buffer) passes through the membrane
- New solvent added to product

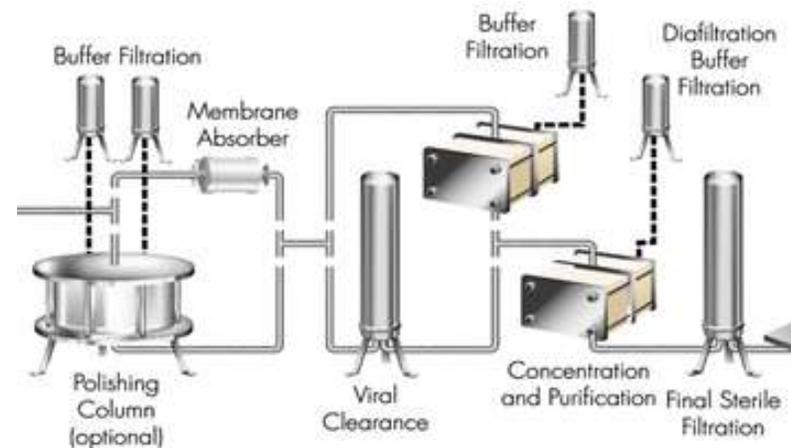


Examples of Uses of TFF UF in Biological Manufacturing Processes

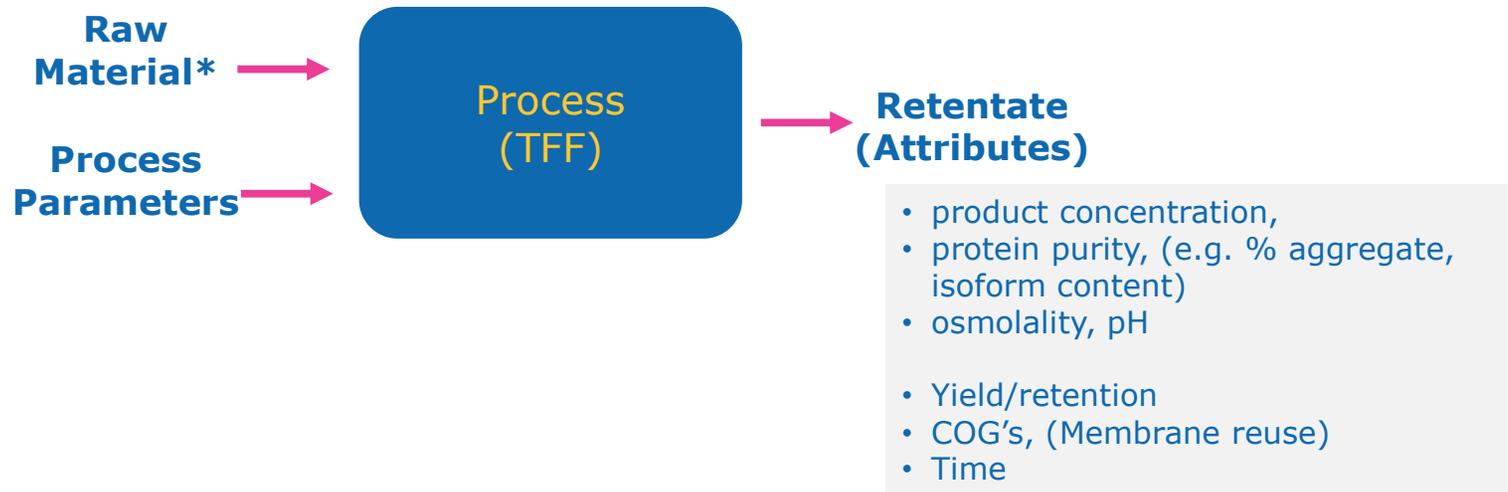


Examples of UF product CQAs in a mAb process

- UF product **CQA's** include:
 - recovered retentate product concentration,
 - recovered retentate protein purity, (e.g. % aggregate)
 - retentate buffer composition, osmolality, pH
-
- Key Process Attributes (**KPA**)
 - Yield/retention
 - COG's, (Membrane reuse)
 - Time (....?)



Link Material attributes and Process parameters to CQA & KPA



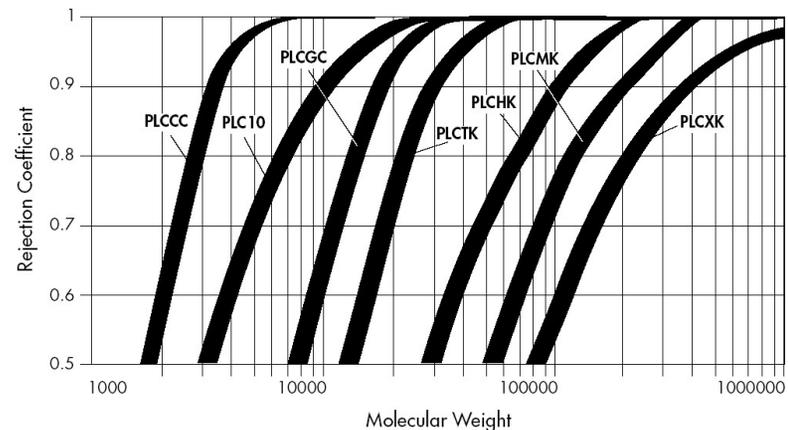
*Raw Material attributes: from Feed solution, buffers



Example of Raw Material attributes in mAb UF/DF process

- From Feed solution
 - Starting concentration
 - pH, conductivity,
 - Feed buffer composition
 - DF buffer
- From Filter
 - Lot number
 - UF Membrane type
 - MWCO
 - Mass transfer coefficient

Input from AEX Step	Output to Final Sterile Filtration
Protein Concentration 8 - 10 g/L	Protein Concentration 150 g/L
pH 7.4 - 7.6	pH 7.4 - 7.7
Aggregate < 0.8%	Aggregate < 0.8%
Acidic Variants ≈ 10%	Acidic Variants ≈ 10%
HCP < 12ng/mg	HCP < 12ng/mg
Buffer A	Buffer B
Other	pH, Osmolality, Surfactant Concentration, acetate, sucrose etc



Example of Process Parameters in TFF UF

Step	Process Parameter(s)
Installation	Module type, area, torque, Hydraulic compression
Flush	L/m ² retentate & permeate water
Integrity test	Test pressure & air flow spec
Equilibration	L/m ² retentate & permeate buffer
Concentration/ Diafiltration	Feed flow & TMP, Loading, concentration end-points & diavolumes, Temperature
Recovery	L/m ² retentate DF buffer
Cleaning	Water flush as above, cleaner type/temp/concentration/time/feed flow, L/m ² loading, NWP measurement conditions and specs
Sanitization	Sanitant type/temp/concentration/time/feed flow, L/m ² loading, environment



**Example of risk
assessment to
categorize UF process
parameters**



Risk Assessment to Classify Process Parameters

- The risk analyses help identify and categorize operating parameters by classifying them into those that are most or least important
- For most important parameters:
 - those that could employ ranges based on prior knowledge, modular claims (from previous products or literature studies)
 - those that need further evaluation (DOE characterization studies: multivariate, univariate),
 - CPP, KPP
 - GPP



Risk assessment

- Scoring of Process Parameters and Quality (& Process) Attributes

Process Parameters		Quality (or Process) Attributes	
Impact Score	Ranking Criteria	Weight Score	Ranking Criteria
10	Strong relationship known based on available data and experience	10	Established or expected direct relationship to product quality or safety (incl. mfg safety)
7	Strong relationship is expected	7	Unsure. Impact to product quality or safety or key business drivers expected
5	Not-so-strong relationship expected or known	5	Unlikely to impact product quality or safety
1	Known to not have a relationship	1	No product or safety impact expected

Cumulative score = \sum (Impact of parameter x Weight of quality attribute)

Source: CMC Biotech Working Group, (October 2009), A-Mab: A Case Study in Bioprocess Development, V2.1



TFF Risk Analysis – Example of a UF-DF

Process & Product Attribute weight score

		Attribute Weight						
		4	5	5	10	7	10	
Phase	Parameter	Process Attribute			Product Attribute			Score
		Step Yield	Membrane Reuse	Process Time	Impurity and/or Contaminant	Protein Content (Retentate conc)	Aggregate	
Conc/Diaf	Feed Flow Rate (LPM/m ²)							0
	Transmembrane Pressure (psi)							0
	Process Loading, L/m ²							0
	No of DiaVolumes							0
	Feed Concentration, g/L							0
	Recovery, L/m ²							0
	Temperature							0

List of all process parameters

List of Quality & Process Attributes



TFF Risk Analysis – Example of a UF-DF

		Attribute Weight						Score
Phase	Parameter	4	5	5	10	7	10	
		Process Attribute			Product Attribute			
		Step Yield	Membrane Reuse	Process Time	Impurity and/or Contaminant	Protein Content (Retentate conc)	Aggregate	
Conc/Diaf	Feed Flow Rate (LPM/m ²)	3	1	5	3	3	1	103
	Transmembrane Pressure (psi)	1	1	7	3	5	1	119
	Process Loading, L/m ²	1	1	7	1	3	1	85
	No of DiaVolumes	3	1	7	7	1	1	139
	Feed Concentration, g/L	1	1	2	1	3	1	60
	Recovery, L/m ²	1	1	1	1	6	1	76
	Temperature	1	1	2	1	2	2	63



TFF Risk Analysis – Example of a UF-DF

		Attribute Weight						Score
		4	5	5	10	7	10	
Phase	Parameter	Process Attribute			Product Attribute			
		Step Yield	Membrane Reuse	Process Time	Impurity and/or Contaminant	Protein Content (Retentate conc)	Aggregate	
Conc/Diaf	Feed Flow Rate (LPM/m ²)	3	1	5	3	3	1	103
	Transmembrane Pressure (psi)	1	1	7	3	5	1	119
	Process Loading, L/m ²	1	1	7	1	3	1	85
	No of DiaVolumes	3	1	7	7	1	1	139
	Feed Concentration, g/L	1	1	2	1	3	1	60
	Recovery, L/m ²	1	1	1	1	6	1	76
	Temperature	1	1	2	1	2	2	63

For Further Evaluation ?



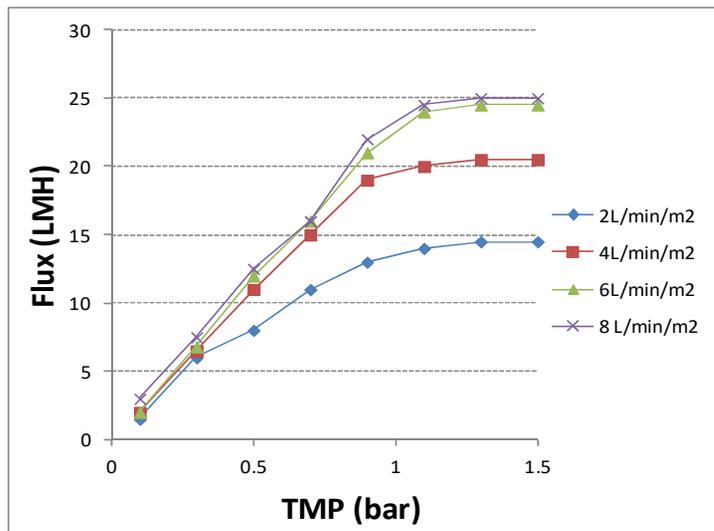
TFF Risk Analysis – Example of a UF-DF

- PD studies to explore characterization range and establish acceptable range for KPPs and CPPs

Parameter	Low	Middle	High	Score	Scientific Rationale
Feed Flow Rate (LPM/m ²)	3,5	5	6,5	103	Impacts polarization, fouling & potentially shear; may impact process time, reuse etc
Transmembrane Pressure (ps)	16	30	45	119	Directly impacts flux, polarization and fouling, and therefore, process time, achievable retentate conc
No of Diavolumes	6	8	10	139	Potential impact on purity & residual buffer levels; DF continuous mode for best efficiency
Feed Stock	2-3 lots representing variability in Feed			Linking Variable	Potential for variability in feed conc, or impurity levels to impact UF-DF performance
Filter	2-3 lots representing variability in Membrane characteristics			Linking Variable	Variability in membrane retention can potentially influence yield, contaminant removal

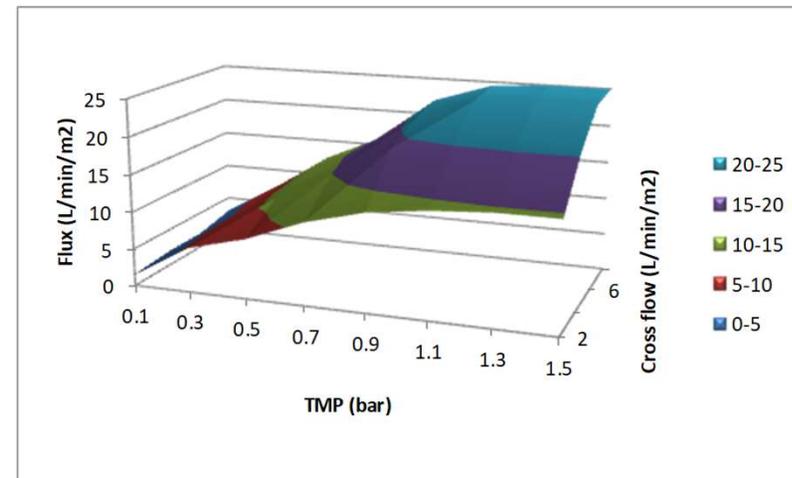


Example of Experiments to Determine Acceptable Range of Process Parameters

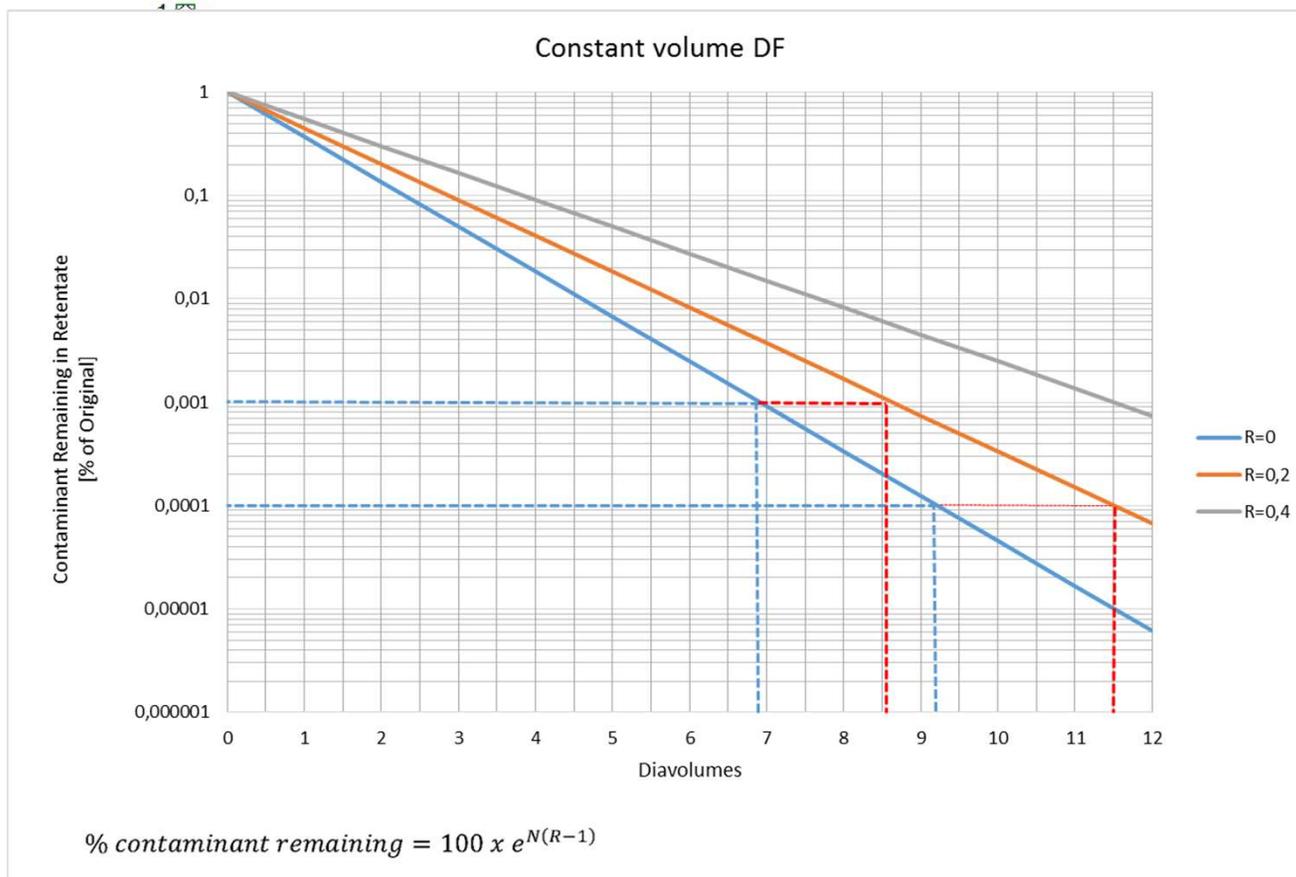


Typical flux excursion experiments have two variables and an output.

- Variables – feed flow rate/cross flow rate and TMP
- Output - Flux



Example of Experiments to Determine Acceptable Range of Process Parameters



A Hypothetical Summary of Process Parameter Classification and Ranges

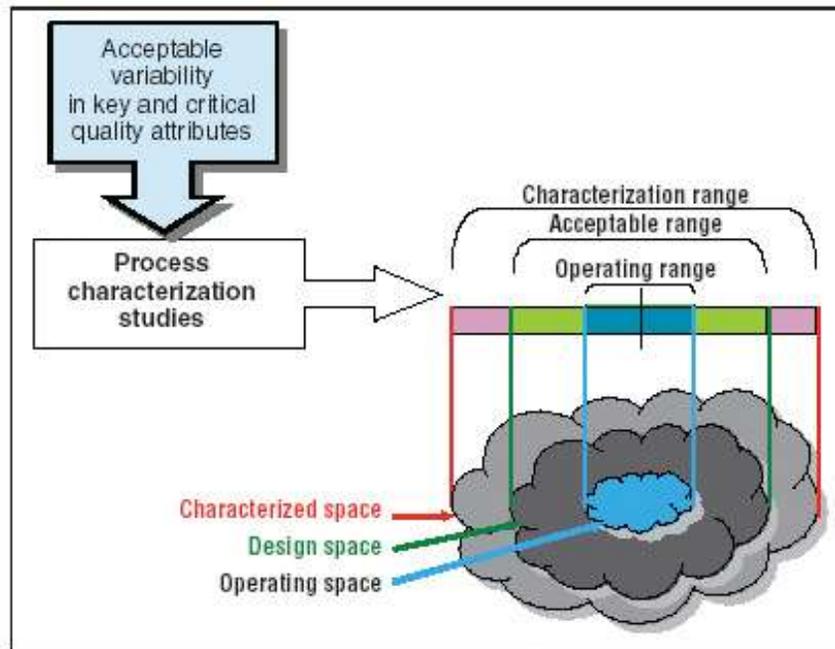
Process Parameter	Acceptable Range	Parameter Classification	Rationale (Justification)	Control Strategy
Feed Flow Rate (LPM/m ²)	3.5-6.5	KPP	DOE	Skid Control
Transmembrane Pressure (psi)	16-45	KPP	DOE	Skid Control
Process Loading, L/m ²	18-42	GPP	DOE	Batch Procedure
No of DiaVolumes	6-10	KPP	DOE	Skid Control
Feed Concentration, g/L	6-14	GPP	Modular (Prior knowledge)	Titre Analysis
Recovery, L/m ²	70-90%	GPP	Modular (Prior knowledge)	Skid Control
Temperature, C	15-25	GPP	Modular (Prior knowledge)	Environmental Control

NB. Above assessment identified there were no CPPs for [this process](#) – may not be applicable in all UF/DF processes



Definition of “window of operation” or operating space

The Process Characterization study helps in the establishment of the design space



Rathore, A.S. et al. (2007) - Design space for biotech products - BioPharm Int. 20 (4), 36-40



Control of Process Parameters

- Control Strategy
 - A method to keep or maintain the 'process' within the design space.
- Ensure product quality and safety (for CPPs)
 - Control within design space to ensure consistent product quality
- Ensure that the commercial manufacturing process is consistent and robust (KPPs)
 - Non CPPs need to be controlled just as much as CPPs do

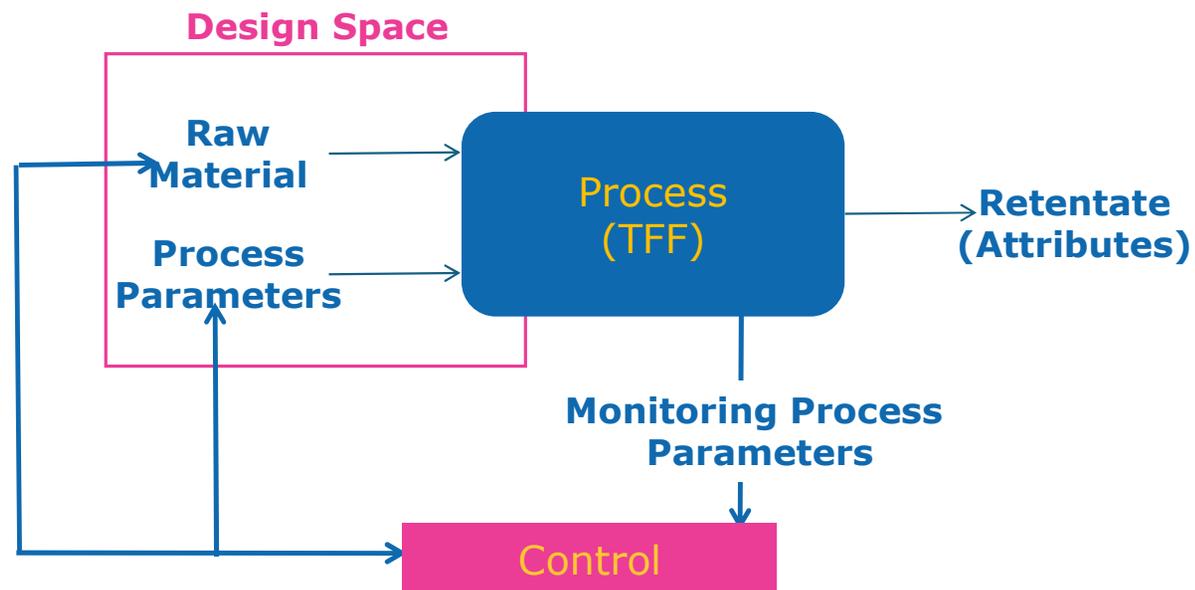


Parameter Monitoring & Control UF Examples

Feed	Feed concentrations of protein product, aggregates, bioburden, and buffer components can be measured directly and/or controlled through the previous step.
Filter	Filter properties such as retention, permeability – monitor through vendor quality audit.
Feed Flow, TMP	Control the feed pump flow using a mass flow meter & PID control. Use retentate flow control valve & pressure transmitters (feed, retentate, permeate) to control TMP (PID).
Concentration End-Point	Retentate tank volume (Wt) or level specification.
Diafiltration End-Point	Maintain diafiltration flow rate = permeate flow rate through retentate level control & use either time or permeate volume measurement.



QbD Concept - Control Strategy



Summary

- QbD represents a scientific approach to build-in & ensure quality in drug substances
 - Emphasizes process understanding, relationship between CPPs, CQAs, QTPPs using a methodical approach (risk assessment)
- QbD principles may be applied to determine the important process parameters
- Process control strategies help ensure that process parameters are maintained within the desired range to ensure product quality and reliable process operation
- Vendors can assist to define process development, characterization & control
 - Deep knowledge of Filter material & attributes



Thank you.
any questions ?



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