Practical example of scaling up a biotech process using QTPPs, CQAs and CPPs

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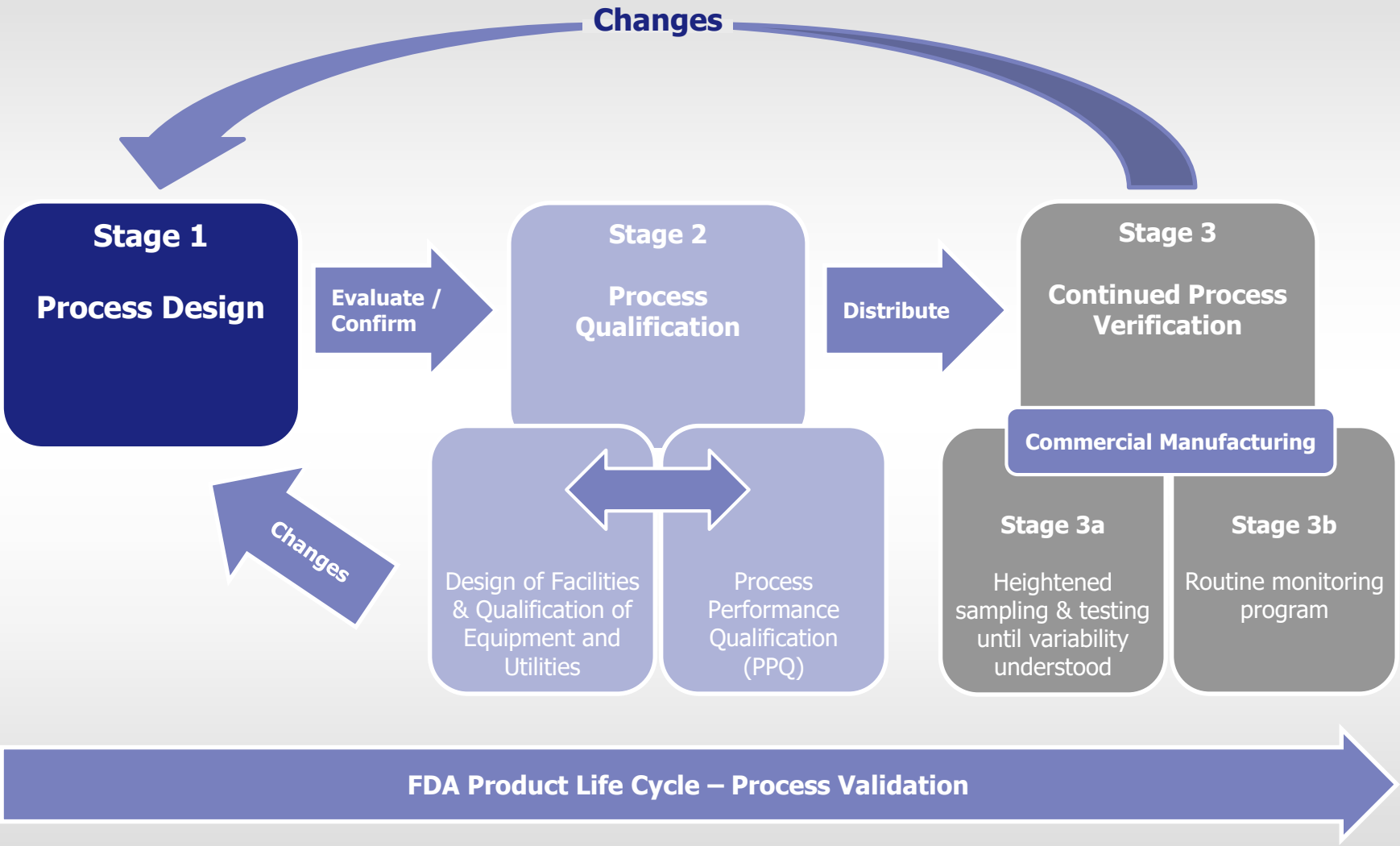
Regulatory Knowledge, Practically Applied.

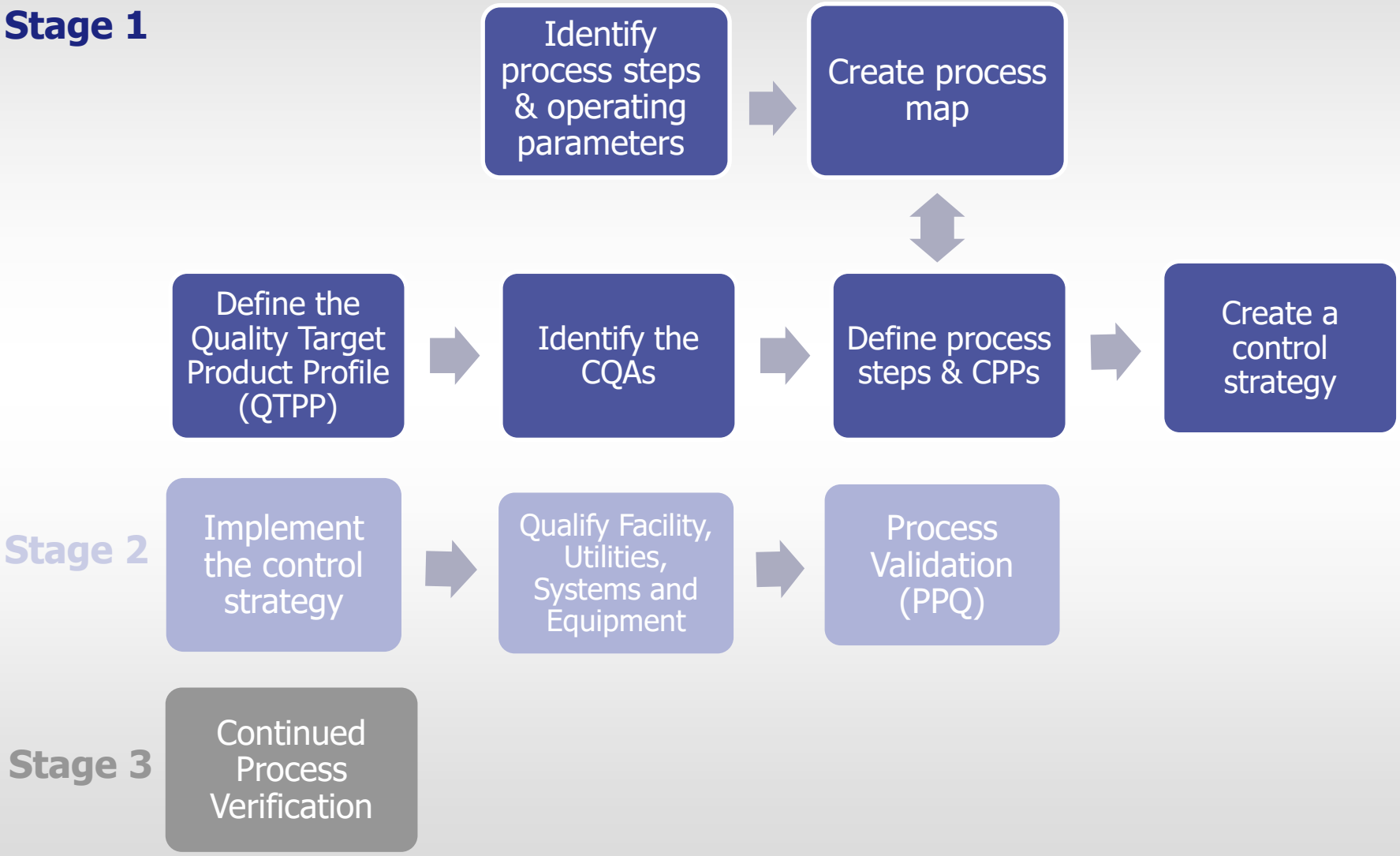
Project objectives

- Manufacture of PharmOtein
- Parenteral protein solution
- Scale up of the manufacturing process from pilot scale (10 L batch size) to production scale (100 L batch size)
- Design and specification of the process equipment

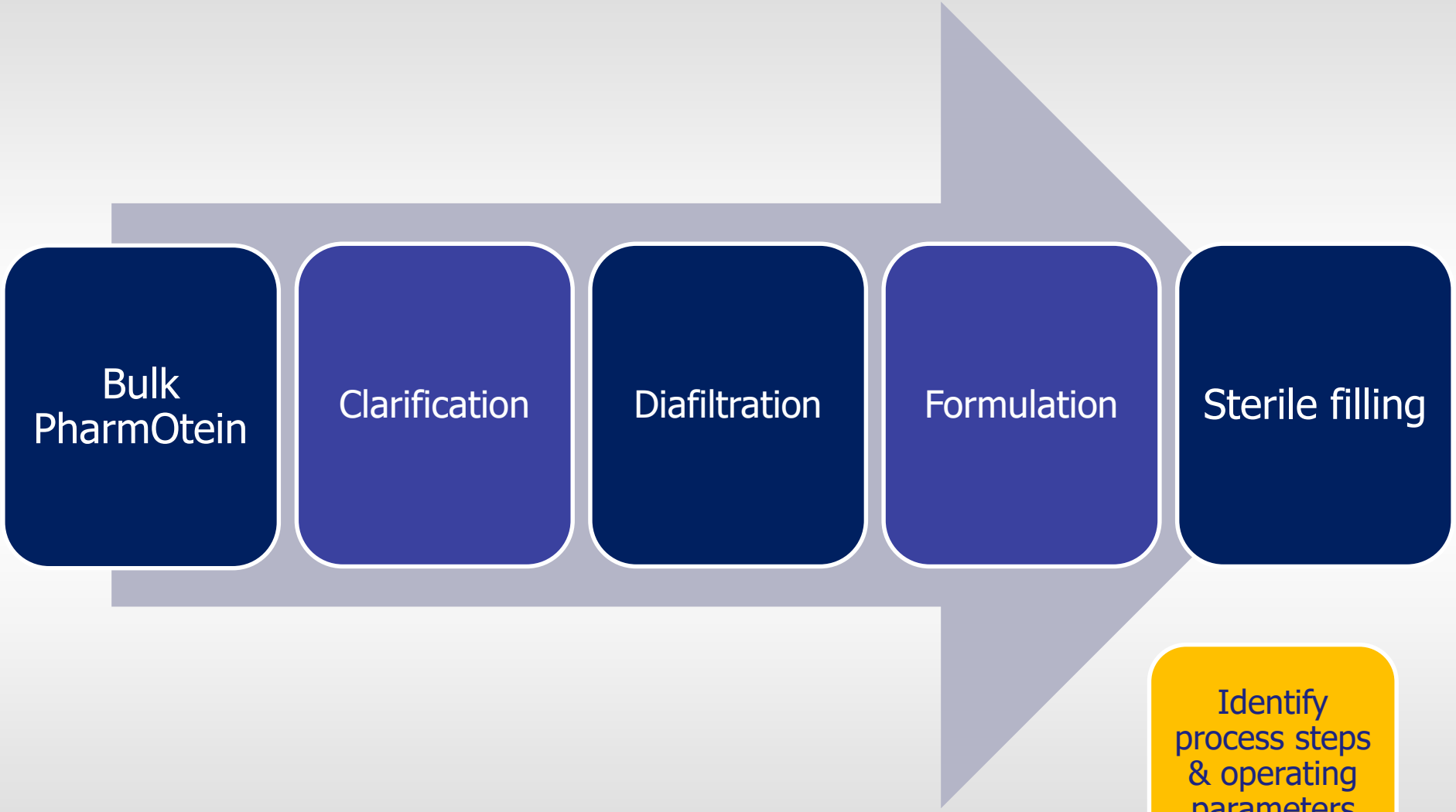
Process validation lifecycle



Manufacturing process scale-up



PharmOtein manufacturing process



Identify process steps & operating parameters

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".

(ICH Q8)

Define the quality target product profile (QTPP)

Quality target product profile (QTPP)

Example: 100mg PharmOtein vial

Attribute*	QTPP
Dosage volume	10 mL
Dose	100mg
Particulates	No visible particles
Chemical purity	pH 6.5 – 7.0 Excipient ≤0.1% Solutes concentration
Biological purity	Meets pharmacopeia requirements for parenteral dosage forms
Aggregate	≤1%

Define the Quality Target Product Profile (QTPP)

**Only a few PharmOtein QTPPs described here*

Critical Quality Attributes (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".

(ICH Q8)

Identify the CQAs

From QTPP to CQAs

Example: 100mg PharmOtein vial

Attribute	PharmOtein QTPP*	Translation to CQA
Dosage volume	10 mL	Fill volume
Dose	100mg	PharmOtein Concentration
Particulates	No visible particles	No observed visible particles
Chemical purity	pH 6.5 – 7.0 Excipient ≤0.1% Solutes concentration	pH Excipient concentration NaCl concentration
Biological purity	Meets pharmacopeia requirements for parenteral dosage forms	Sterility
Aggregate	≤1%	Aggregate concentration

Identify the CQAs

**Only a few PharmOtein QTPPs & CQAs discussed here*

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Process step impact

CQA	Clarification	Diafiltration	Formulation	Sterile filling
Fill volume				✓
PharmOtein concentration		✓		
Visible particles	✓			
pH		✓		
Excipient concentration			✓	
NaCl concentration		✓		
Sterility				✓
Aggregate concentration	✓			

✓ Known or potential impact to CQA

Define process steps & CPPs

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Identify Operating Parameters

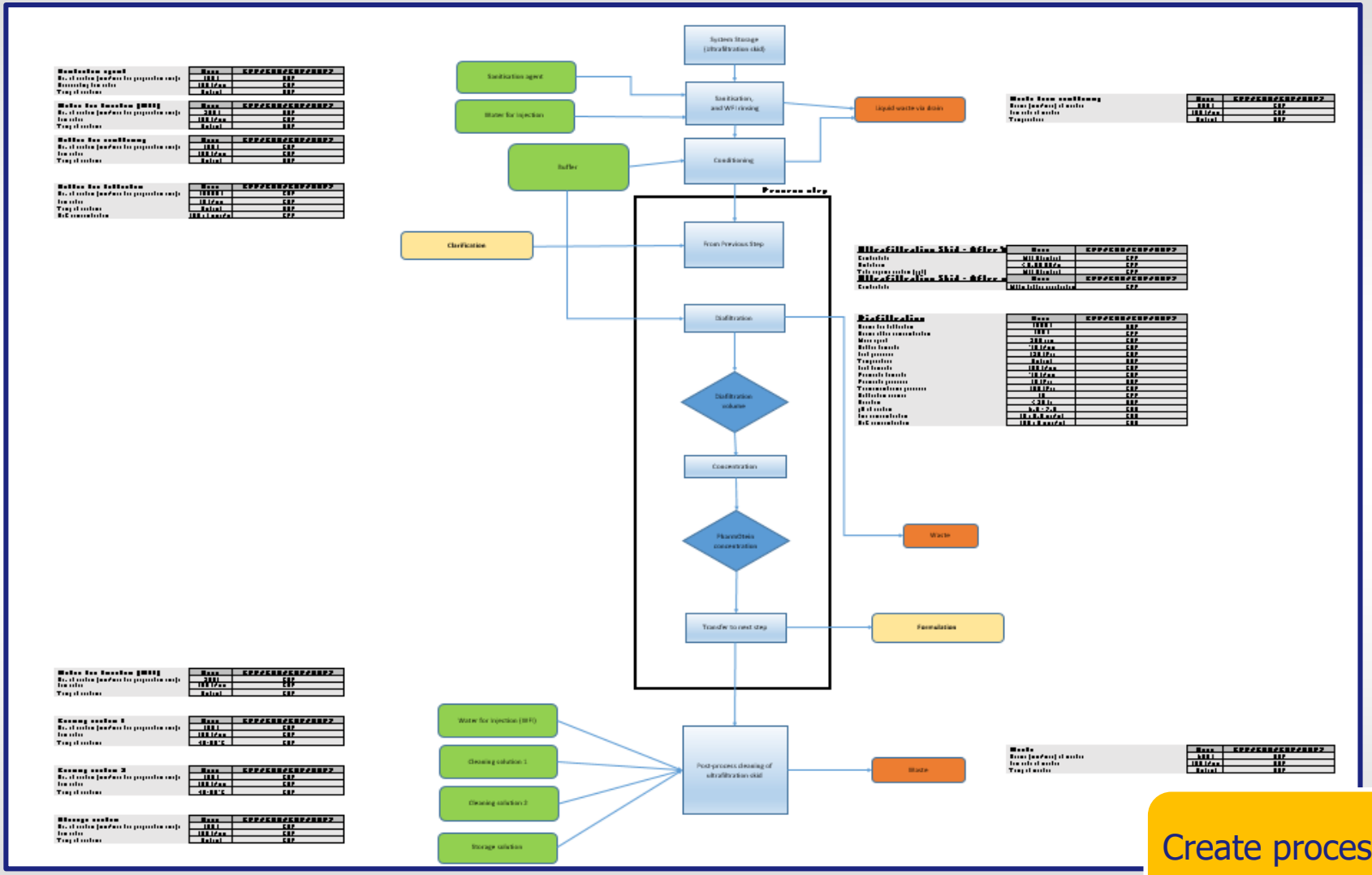
Example: Diafiltration

Operating Parameter*	Value
Volume for diafitration	1000 L
Volume after concentration	100 L
Mixer speed	200 rpm
Buffer flowrate	~10 L/min
Feed pressure	120 kPag
Temperature	Ambient
Feed flowrate	100 L/min
Permeate flowrate	~10 L/min
Permeate pressure	10 kPag
Transmembrane pressure	100 kPag
Diafiltration volume:	10
Duration	< 20 hr
pH of solution	6.5 - 7.5
Final concentration	10 ± 0.5 mg/mL
NaCl concentration	100 ± 1 mmol/mL

**Only a few PharmOtein parameters discussed here*

Identify process steps & operating parameters

Process map - Diafiltration



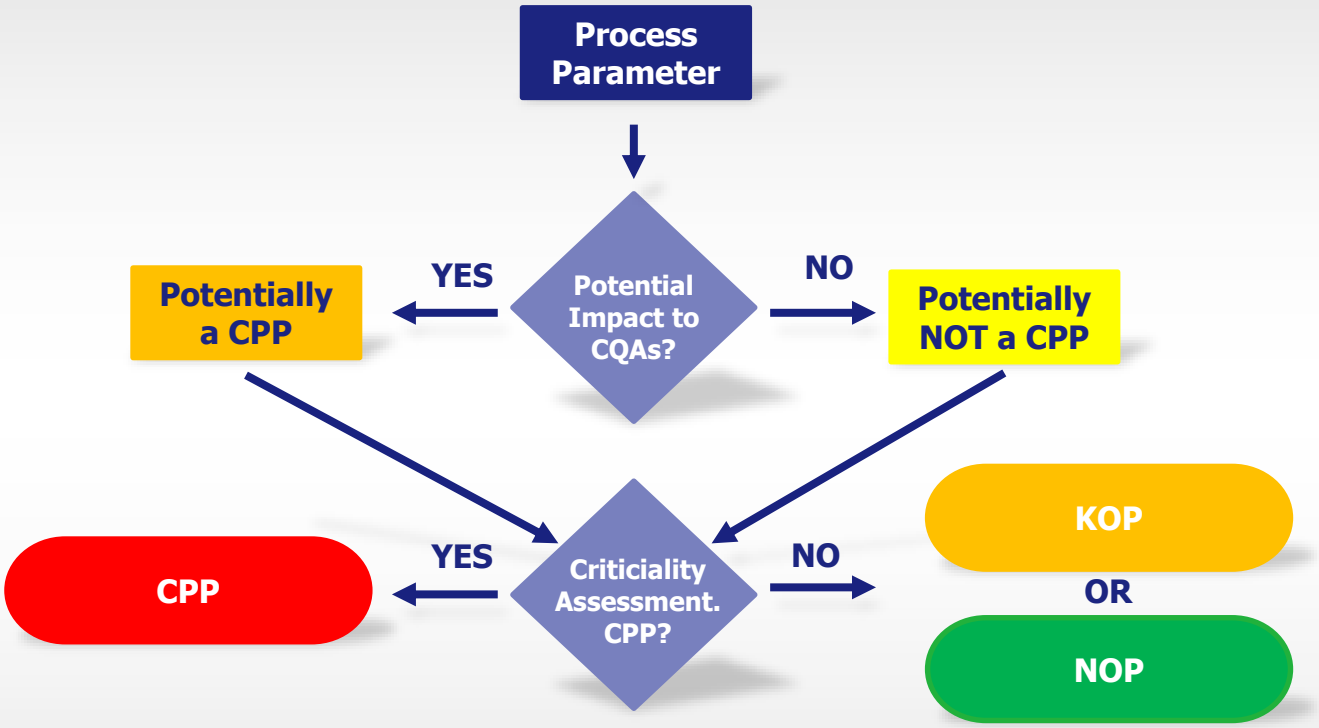
Create process map

Parameter definitions

CPP	Critical Process Parameter	• A process parameter whose variability impacts a quality attribute and therefore needs to be controlled to ensure the process produces the desired quality. • A critical process parameter remains critical even if it is controlled.
KOP	Key Operating Parameter	A process parameter whose variability affects the desired operability of the system or equipment to produce the desired output but has no impact on a quality attribute.
NOP	Normal Operating Parameter	A process parameter whose variability has no impact on the desired operability of the system or equipment to produce the desired output as well as a quality attribute.

Define process steps & CPPs

Defining CPPs, KOPs, NOPs



Define process steps & CPPs

The PharmOut "STIC-man"

Summary **T**able from **I**shikawa **C**riticality-**man**!

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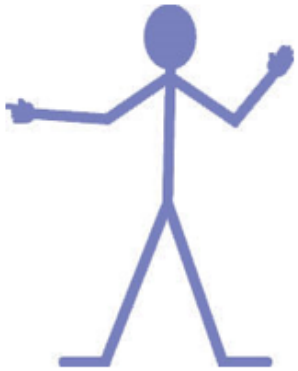
PharmOtein Criticality Assessment

CQA # NaCl concentration

Diafiltration Step

PP #	Criticality	Process Parameter
1	KOP	Mixer speed
2	KOP	Buffer flaurate
3	KOP	Feed pressure
4	KOP	Feed flaurate
5	KOP	Permeate pressure
6	KOP	Transmembrane pressure
7		
8		
9		
10		

Machine



Method

Process Parameter	Criticality	PP #
Volume for diafiltration	KOP	21
Diafiltration volume	CPP	22
Duration	NOP	23
		24
		25
		26
		27
		28
		29
		30

PP #	Criticality	Process Parameter
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		

Man

Materials

Process Parameter	Criticality	PP #
Buffer NaCl concentration	CPP	31
		32
		33
		34
		35
		36
		37
		38
		39
		40

INSTRUCTIONS

List the process parameters in the Machine, Method, Man and Materials tables
Assess the impact of variability on the CQA

CPP	*Variability will affect the CQA*
KOP	*Variability affects the desired operability of the system or*
NOP	*Variability has no impact on operability of the system or CQA*

Define the Quality Target Product Profile (QTPP) → Identify the CQAs → Define Process Steps & CPPs → Create a Control Strategy

Define process steps & CPPs

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Define parameters

Example: 100mg PharmOtein vial, Diafiltration

Operating Parameter*	Value	Parameter Type
Volume for diafiltration	1000 L	NOP
Volume after concentration	100 L	CPP
Mixer speed	200 rpm	KOP
Buffer flowrate	~10 L/min	KOP
Feed pressure	120 kPag	KOP
Temperature	Ambient	KOP
Feed flowrate	100 L/min	KOP
Permeate flowrate	~10 L/min	KOP
Permeate pressure	10 kPag	NOP
Transmembrane pressure	100 kPag	KOP
Diafiltration volume:	10	CPP
Duration	< 20 hr	NOP
pH of solution	6.5 - 7.5	CQA
Final PharmOtein concentration	10 ± 0.5 mg/mL	CQA
NaCl concentration	100 ± 5 mmol/mL	CQA

Define process steps & CPPs

**Only a few PharmOtein parameters discussed here*

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Control strategy

"A planned set of controls, derived from current product and process understanding that ensures process performance and product quality."

(ICH Q10)

Create a control strategy

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Control strategy

- Will ensure that the process remains in control
- Encompasses all elements of each unit operation of the manufacturing process
- All product attributes and process parameters should be in a complete Process Control Strategy
- Only CPPs require validation and should lead to deviations during production

Create a control strategy

Control strategy

Example: Diafiltration

Parameter	Parameter Type	Specification	Control
Diafiltration volume	CPP	10	>10
Buffer NaCl concentration	CPP	95 – 105 mmol/mL	99 – 101 mmol/mL
Feed flowrate	KOP	N/A	90 – 110 L/min
Transmembrane pressure	KOP	N/A	95 – 105 kPag
Permeate flowrate	KOP	N/A	8 – 12 L/min
Final PharmOtein concentration	CQA	9.5 – 10.5 mg/mL	9.8 – 10.2 mg/mL

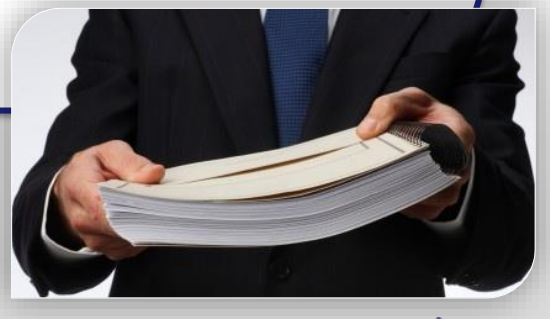
Create a control strategy

** Only a few PharmOtein parameters included here*

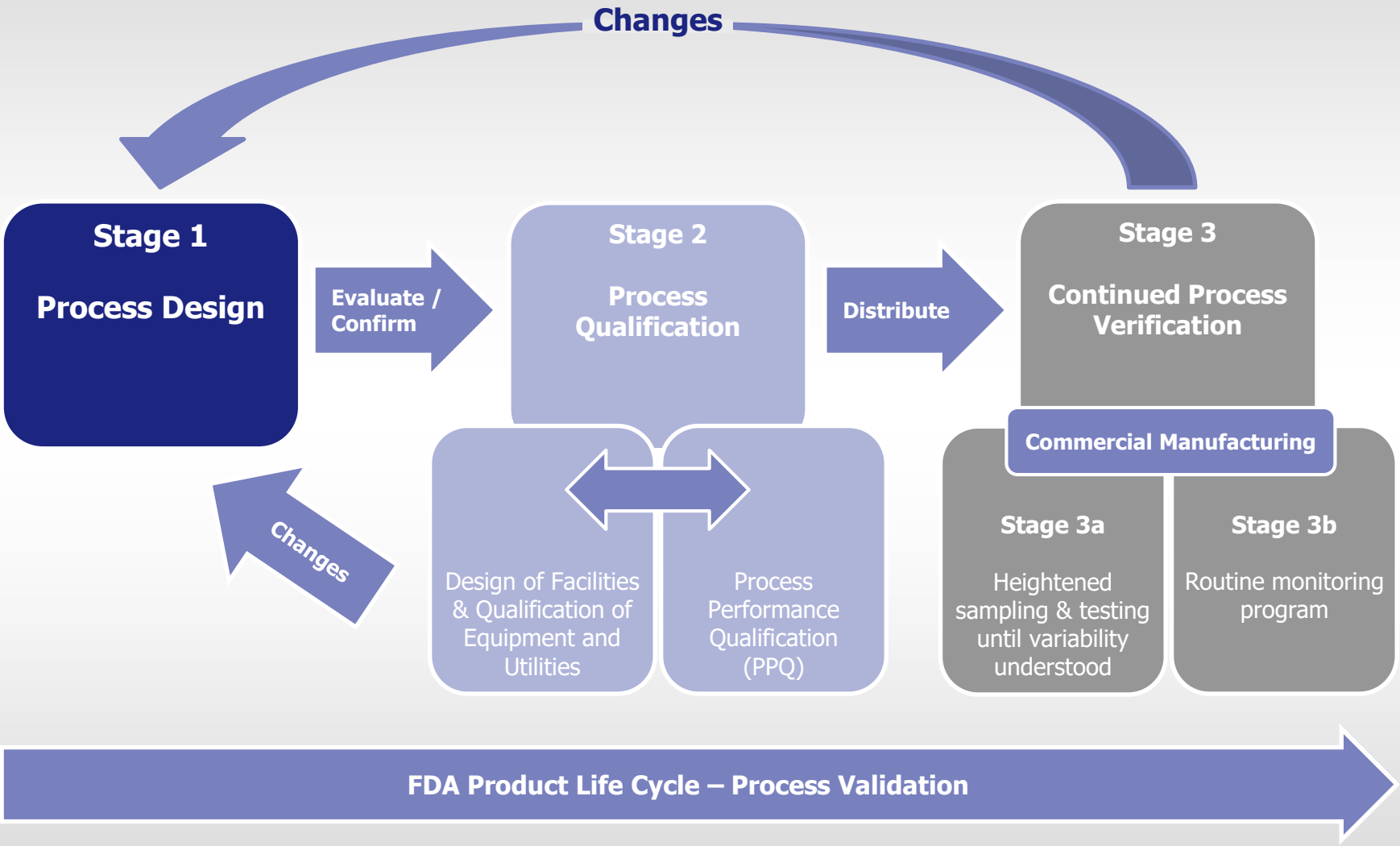
Process design completion

Stage 1 output should be a Report that justifies the Control Strategy:

- Defined CQAs, CPPs and other parameters
- Risk Assessments
- Process Information (Inputs & Outputs)
- Parameters and Ranges



Process validation lifecycle



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Thank you for your time.
Questions?

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