Préservation de la sécurité du patient : Impacts de la définition du procédé à la production en continue d'anticorps monoclonaux

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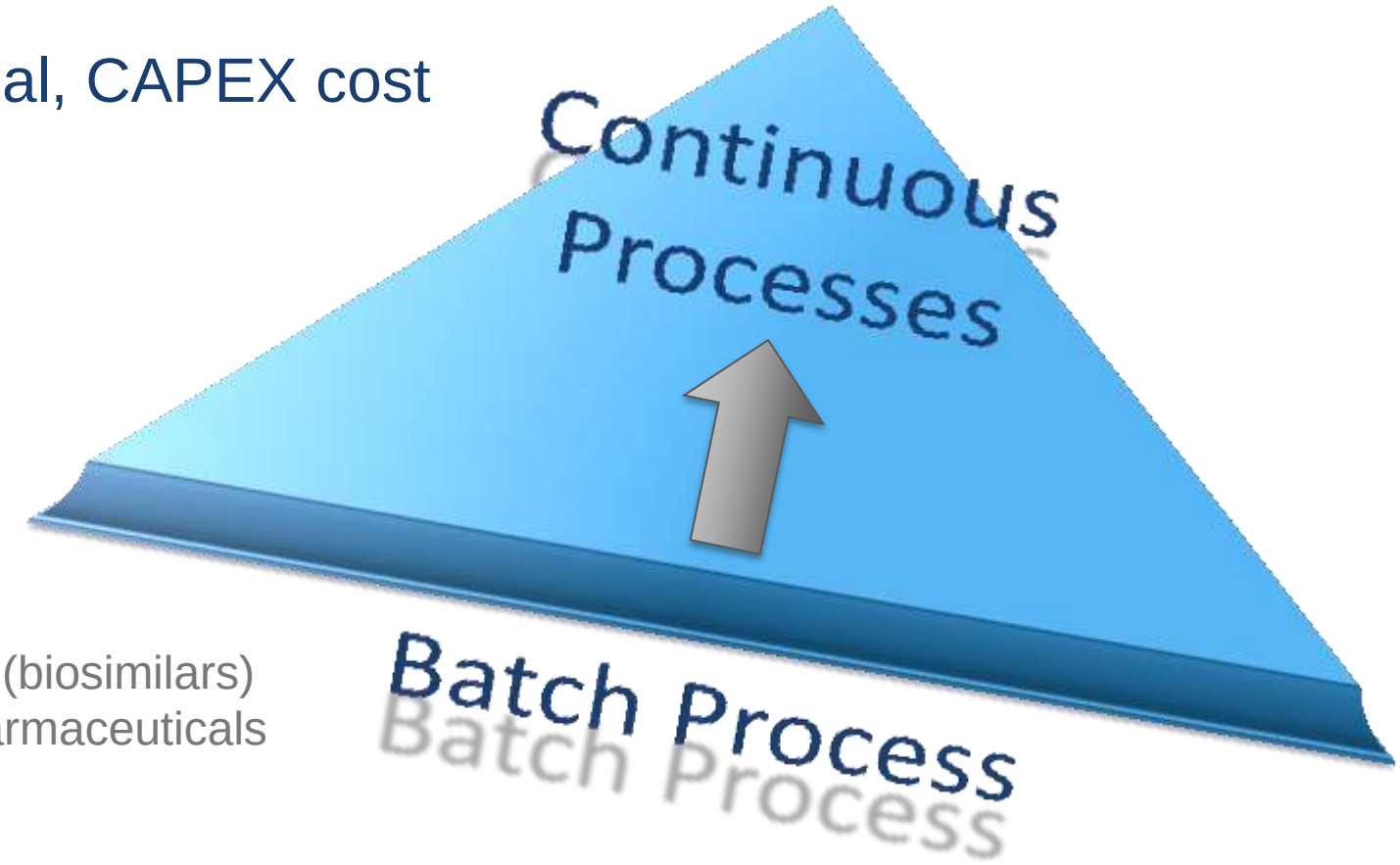
Introduction

- Reduction of raw material, CAPEX cost
- Process simplification
- High Throughput



- Benefits
  - Savings for production costs (biosimilars)
  - enlarge the access to Biopharmaceuticals
- Different approaches
  - Continuous steps
  - Periodic steps
  - Fully integrated tests

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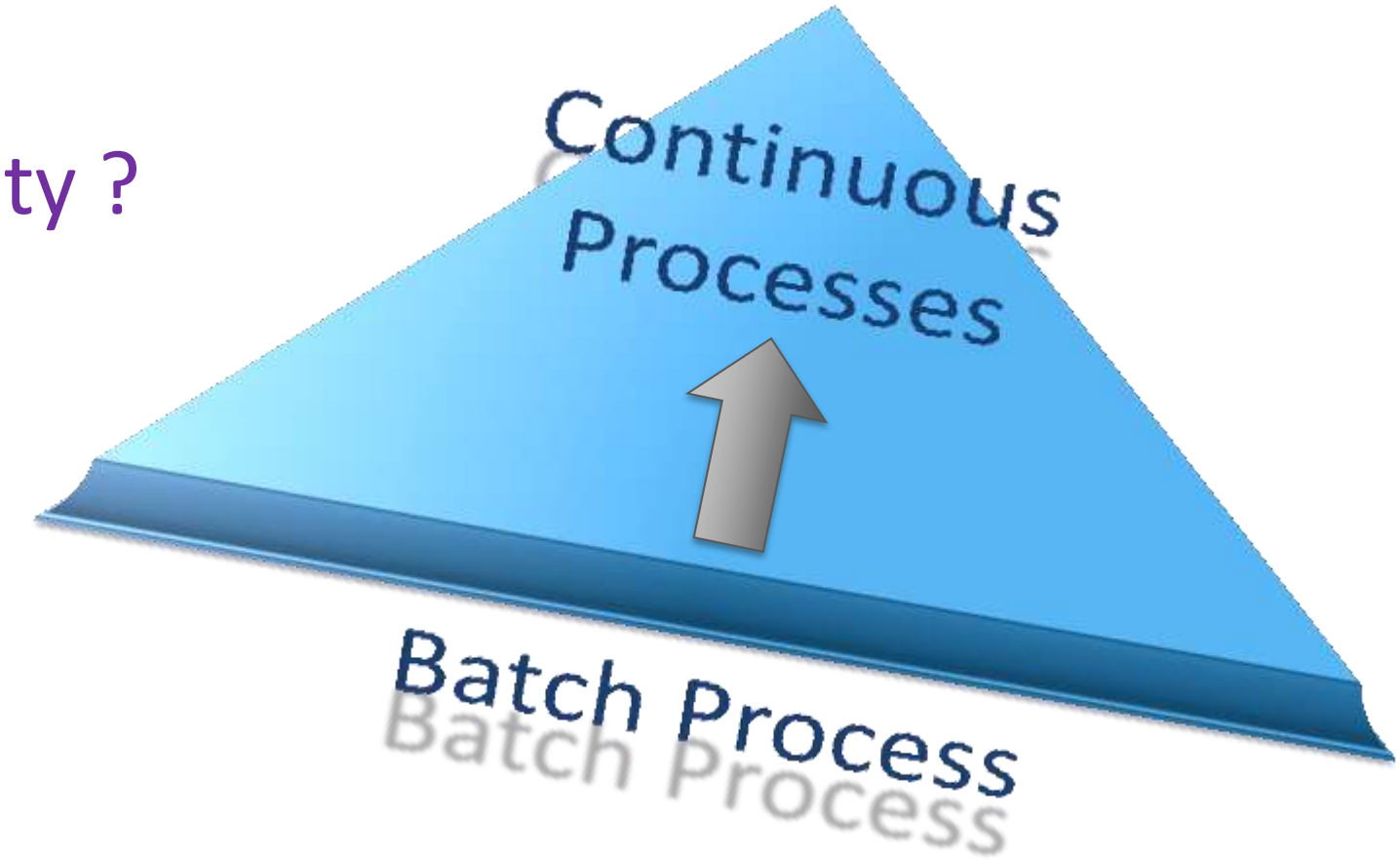
Introduction

Patient Safety ?



Case study of the use of continuous chromatography for mAb purification

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Outline: Continous process for mAb purification

- BioSC® & Multi-columns continuous chromatography
- mAb purification plateform based on continuous chromatography
- Patient Safety
  - Regulatory Perspectives
  - Process Performances & Controls
  - Viral Clearance

BioSC®, Multi-columns continuous chromatography

- **Continuous** chromatography solution to **Capture**
- Adapted equipment to perform **classic bind/elute steps**
- Use of total of the resin **static capacity**
- Standard Process: Five steps
  1. Load of the crude
  2. Wash of the less retained species
  3. Elution of the targeted compound
  4. Regeneration
  5. Equilibration

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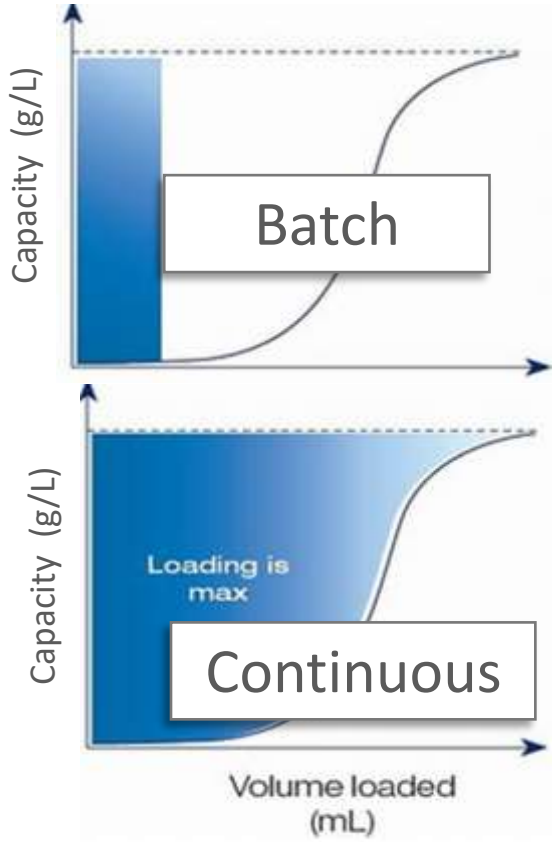
Advantages of BioSC® vs Batch chromatography

- Production cost (resin, buffer…) reduction
- Productivity and time to market optimization
- System size and footprint reduction
- Streamlining processes



BioSC® Lab

BioSC® Pilot

Industrial Scale Continuous Chromatography

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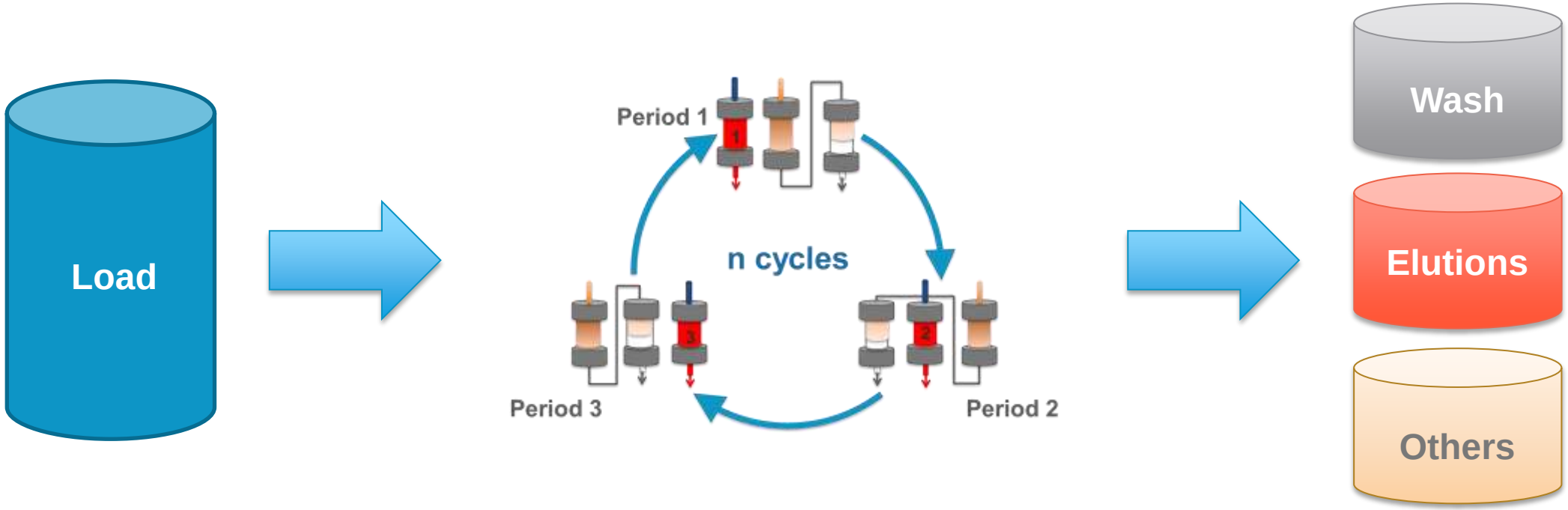
Multi-columns continuous chromatography principle



Operating in steady state

- ✓ Same critical attributes during the run
- ✓ Specific characterization of start and end of production (~ 1 cycle)

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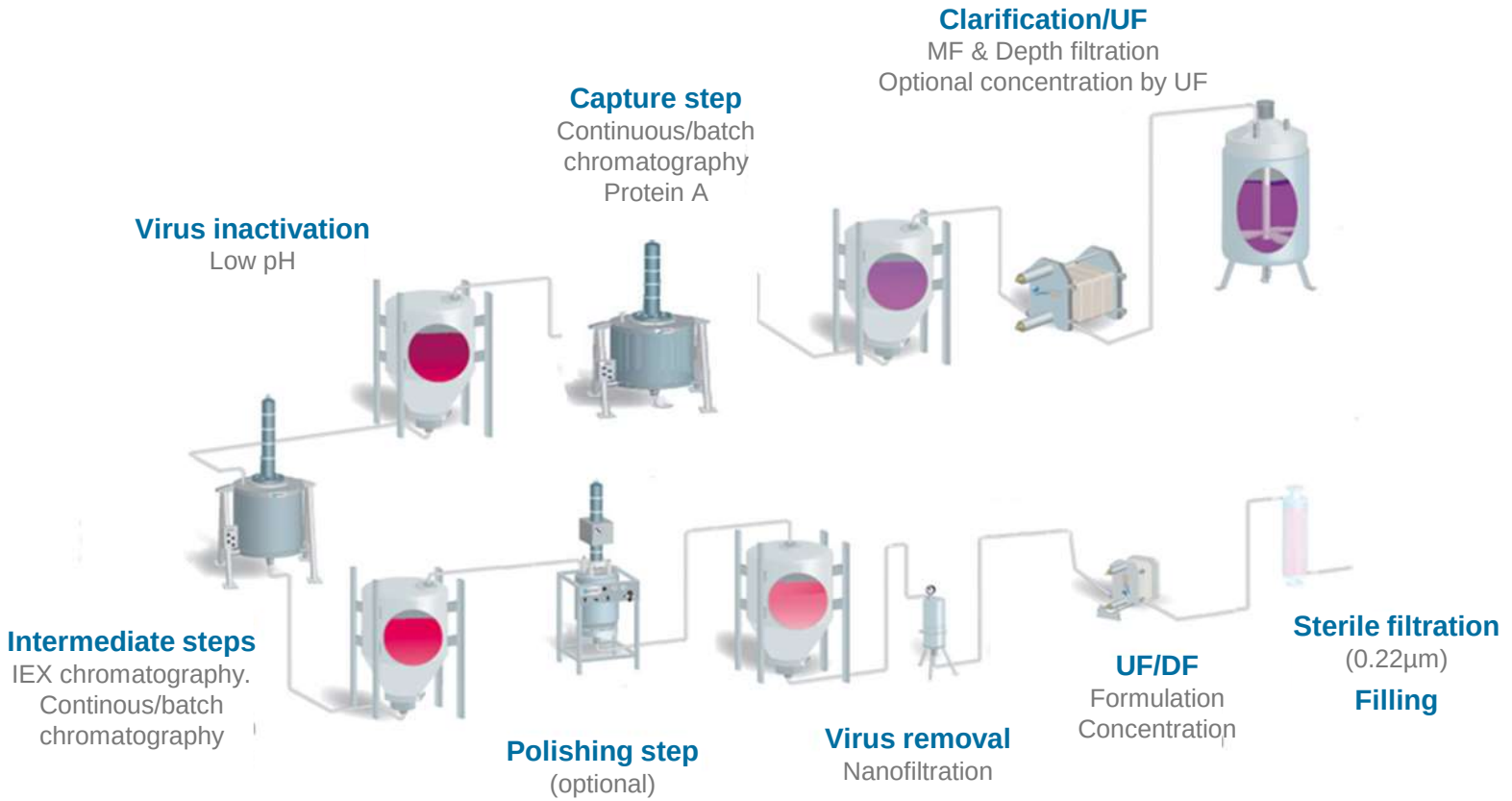
Case study of mAb continuous purification

Standard Batch Process



Case study of mAb continuous purification

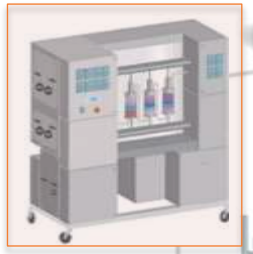
Patient Safety ?

Clarification/UF
MF & Depth filtration
Optional concentration by UF

2 Kg/L/day
Yield: 92,2%

Capture step

Virus inactivation
Low pH



Intermediate steps

3,1 Kg/Lr/day
yield: 85,4%

(optional)

10 MV/min
yield: 97,8%

Virus removal
Nanofiltration

UF/DF
Formulation
Concentration

Sterile filtration
(0.22µm)

Filling

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Regulatory perspectives

CFR 210.3.

- ***Batch**: a **specific** quantity of a drug (..) intended to **have uniform character and quality** (…) and is produced according to a single manufacturing order during the **same cycle of manufacture***
- ***Lot:** a batch, or a specific **identified portion of a batch**, (…), or, in the case of a drug product produced by **continuous process**, it is a specific identified amount **produced in a unit of time or quantity** (…)*

✓ Batch & lot: definition fully applicable

✓ No specific regulations nor guidance's

Steady state : the KEY factor to control

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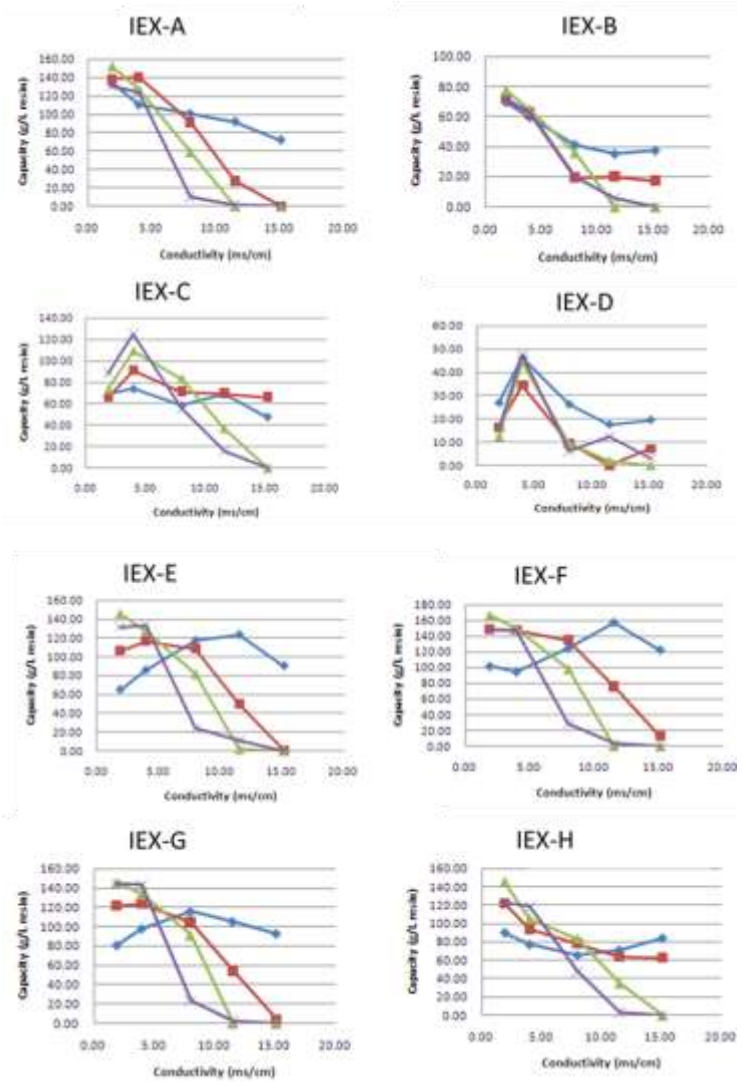
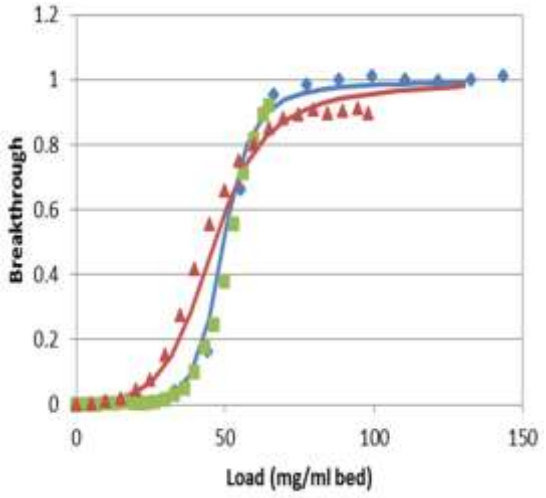
Process design & control to insure same CQAs

Quality Attributes	Impact
Aggregation	Enhanced immunogenicity
Glycosylation	Affect ADCC
Non-Glycosylated Heavy Chain	Impact ADCC
Galactosylation	Galactosylation (%G0, %G1 and %G2) can affect CDC & ADCC
Sialylation	Sialylated forms can impact PK and ADCC
Afucosylation	Afucosylation of IgG1s correlates with ADCC
High mannose	afucosylated forms impact ADCC
Host Cell Protein (HCP)	Inflammatory
DNA	Oncogen transfer (> 60pb)
Amino acid modification	Dependent of the location (CDR, Fc…)
Deamidation	Common at Asn/Gln
Oxidation	
C-terminal Lysine Truncation	Impact on pharmacokinetics
Leached Protein A	Immunogenic and mitogenic effects

Process design requirements



- ✓ Standard approach as for batch for process development
  - CPPs and CQAs
  - Design space
  - Single column approach
- ✓ Specific items to support switch to continuous
  - Breakthrough curves for static binding capacity
  - Process modelization : robustness and optimization
    - Maximize media and buffer savings
    - Maximize productivity



BioSC® Predict: Convert batch recipe to continuous processes smoothly!

Winner Pharmaceutical Engineering

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Process control

Ensure that CQAs are within the appropriate range

Continuous monitoring of steady state

Understanding of the sources of variability of a CQA

✓ Standard risk management approach

In Process controls
Process Analytical Technology (PAT)

✓ Specific hardware features

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Critical Quality Attributes

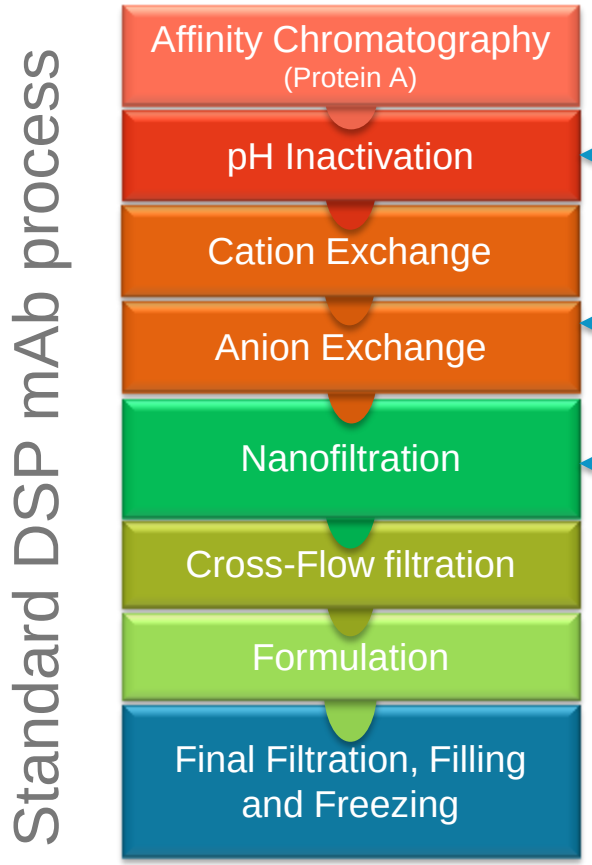
Case study of mAb continuous purification

	Feed	Std spec.	Continuous process
IgG purity (%)	12.2-15.9	>95	**97,8**
Aggregates purity (%)	4.7-9.4	< 3	**2,2**
HCP (ppm)	~200,000	< 5	**< 2**
DNA (ppm)	~4,000	< 10	**1**

✓ Product Quality unchanged with a continuous process

✓ Potential positive impact (unstable proteins)

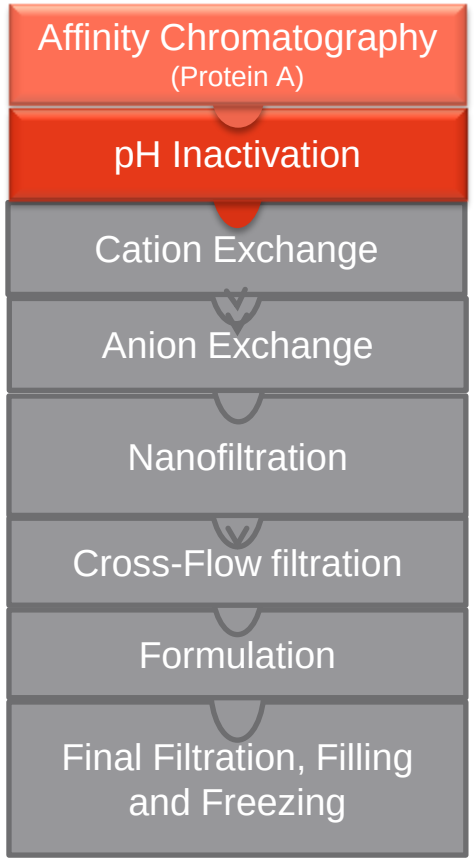
Managing viral clearance
Case of mAb DSP from CHO



- Viral risk
  - Non pathogenic rodent retrovirus
  - Model virus : retrovirus (XMuLV)
- Standard viral clearance steps
  - pH inactivation (virus inactivation)
  - Nanofiltration (virus retention)
  - Optional: chromatography step
- Virus clearance validation
  - Scale down model
  - Spiking studies

Managing viral clearance
pH inactivation: Batch process

Standard DSP mAb process



- Batch inactivation
- CPPs:
  - pH
  - mAb concentration
  - Temperature
  - Incubation time
- Worst-case conditions can been identified
- Scale-down model: efficient mixing within the established time limits

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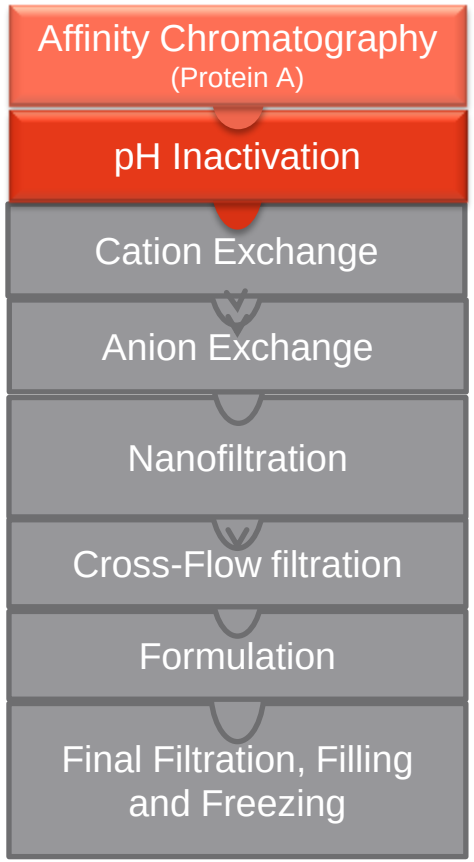
Managing viral clearance
pH inactivation: **BioSC® process**

Standard DSP mAb process



- **Carrousel** of batches
- CPPs: **Identical**
  - pH
  - mAb concentration
  - Temperature
  - Incubation time
- worst-case conditions: **Identical**
- Scale down model: **Identical**

Sequential drums rotation while purification process is at steady state

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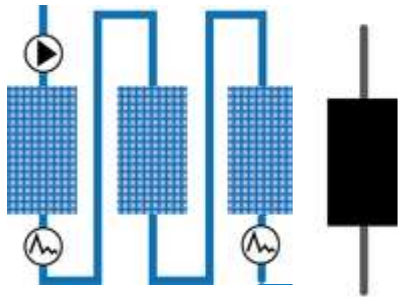
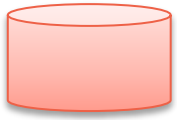
Managing viral clearance
pH inactivation: Type of processes

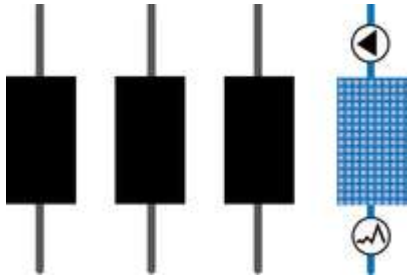
Protein A affinity:
BioSC® 3- column

pH Inactivation

Ion Exchange chromatography







Feed titer	1,76 g/L
nb Elution/cycle	3
Cycle time	105 min.
Time interval/elution	35 min.
Eluted vol/period (300 mm col.)	49,5 L

Min. incubation time	60 min.
Max. holding time	180 min.

Loading time	41 min.
Cycle time	129 min.
Loaded capacity	48 g/Lr

Two options: pH neutralization or direct injection of IEX

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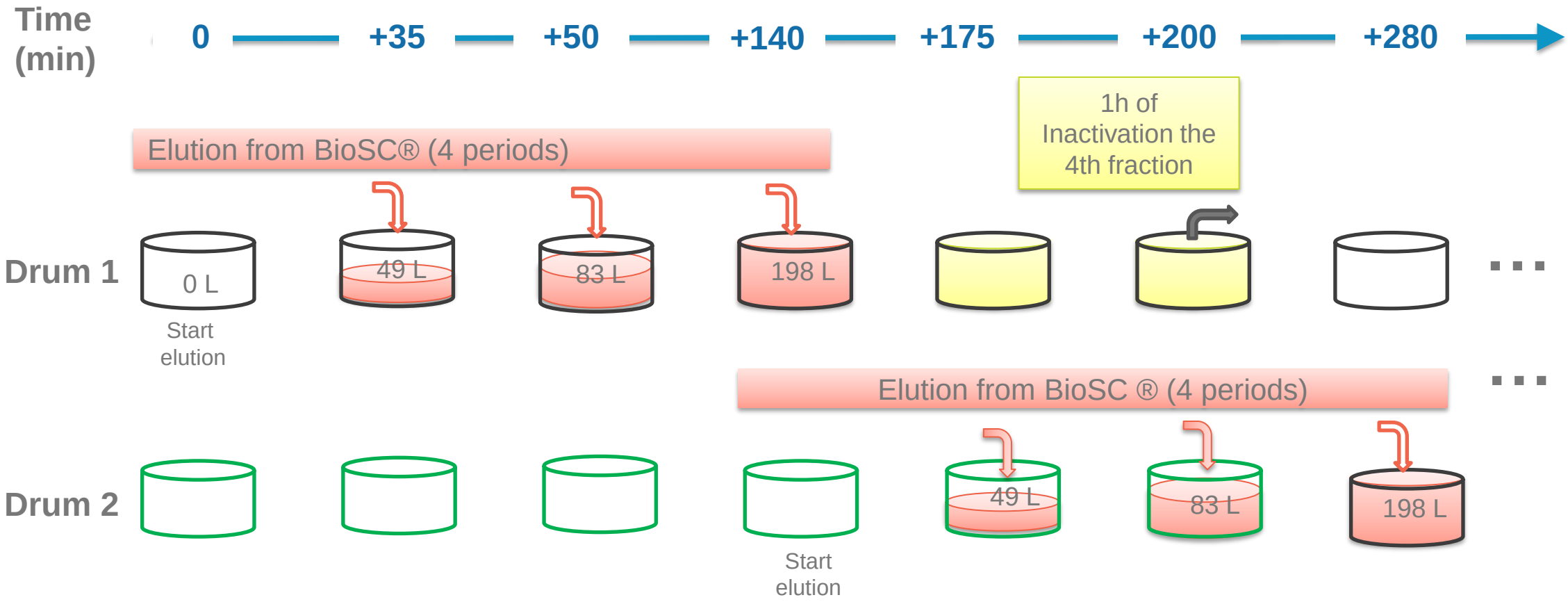
Managing viral clearance

Model case #1 : pH inactivation & neutralization



- ✓ 2 x ~200L drums : Switch every 140 min & Interswitch: 80 min
- ✓ Min. inactivation time (60 min) <t+200 min< max. holding time

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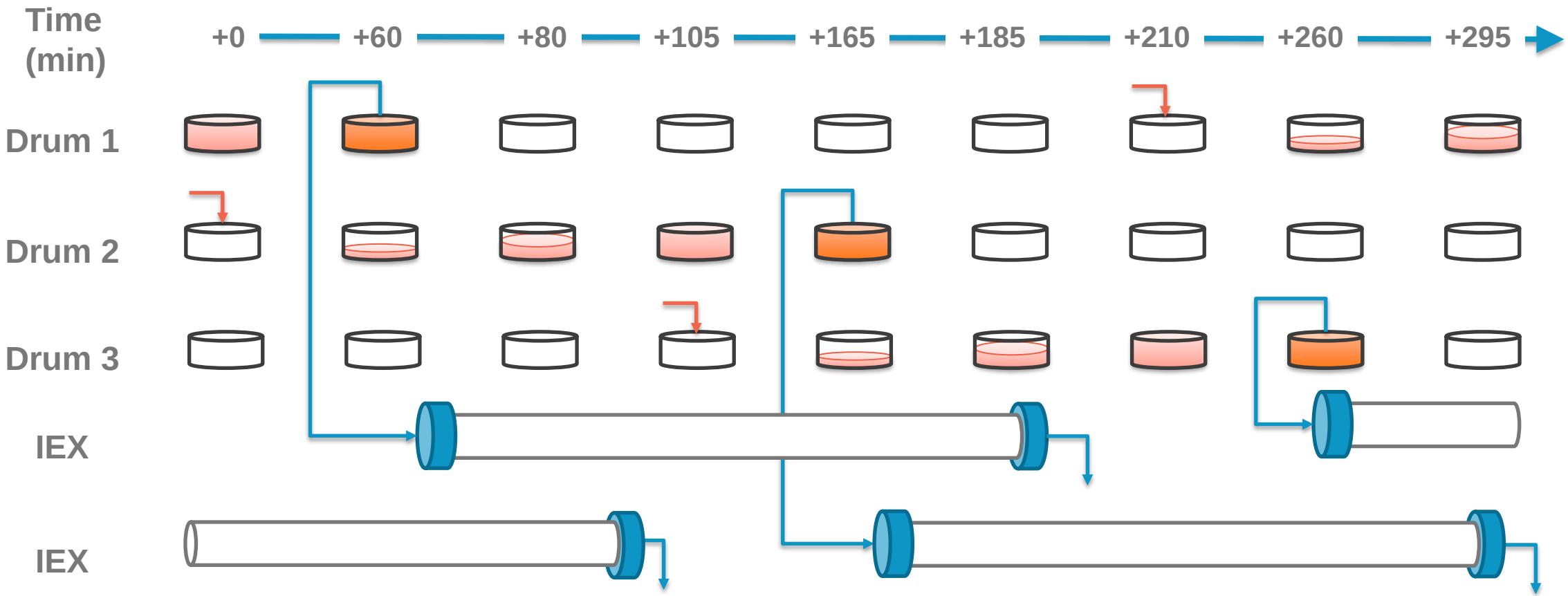
Managing viral clearance

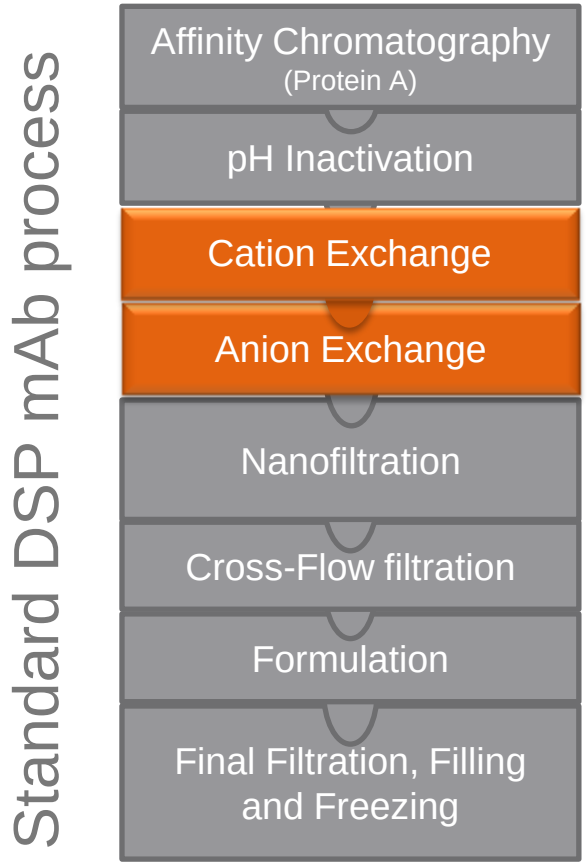
Model case #2 : pH inactivation followed by IEX



- ✓ 3 x ~ 200 L drums : Switch every 105 min & inter-switch: 110 min
- ✓ IEX start: every 129 min.
- ✓ End of inactivation time: 165 min

Managing viral clearance

Viral clearance by chromatography: Batch

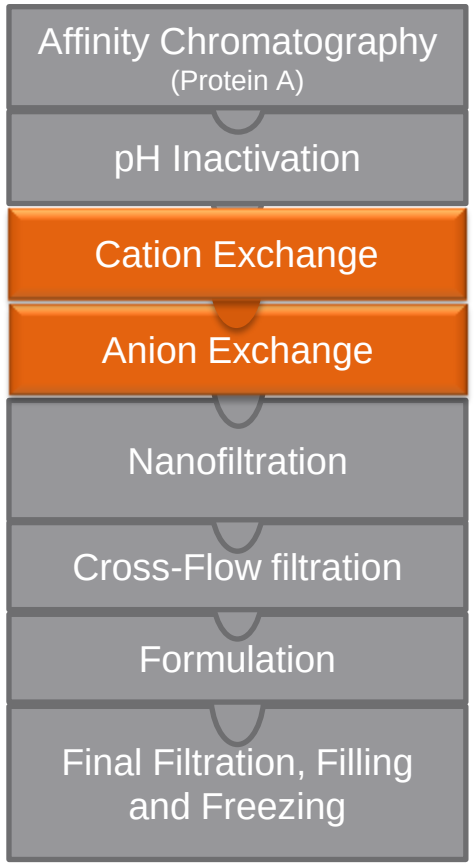


- Parameter classifications and range
  - CPPs
  - Design Space
- Life time study
  - One column study
  - >200 cycles
  - Impact on process performance or impurity clearance over time
- Scale-down model & spiking study
  - One column study
  - LRV > 4

Managing viral clearance

Viral clearance by chromatography: **BioSC® process**

Standard DSP mAb process



- Parameter classifications and range
  - CPPs
  - Design Space
  - **Static binding capacity**
  - **Steady state**
- Life time study
  - One column study
  - >200 cycles
  - **Adaptation of study (70-80% loading vs 10%)**
- Scale-down model & spiking study
  - **Specific to continuous process**
  - Designed in collaboration with **Texcell**

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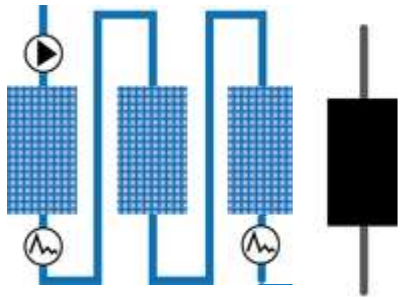
Managing viral clearance

BioSC® downscale model for viral clearance

Process: IEX

BioSC® 3- column



Bed height	10 cm
Load/cycle (Bed volume)	29
Elution/cycle (Bed volume)	6
Cycle time	116 min

Downscale model

BioSC® 3- column

- ✓ Standard scale-down consideration (constant height, linear velocity…)
- ✓ Steady state consideration

Bed height	10 cm.
I.d. columns	1,1 cm
Load/cycle	827 ml
Elution (Bed volume)	171 ml
Cycle time	116 min.

- Start of production ~0, 5 cycle: no spiking
- **Steady-state: 3 cycles**
- End of production ~0,5 cycle: no spiking

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Managing viral clearance
BioSC® downscale model: viral challenge

- Procedure
  - 1% Spiking (~ 8 ml of viral. solution à 10^7 TCID50/ml) of the load
  - Spiking at each period
  - Operation time: < 1 day
  - Equipment: mobile BioSC® Lab
- Results
  - Results in triplicate: 3 LRV
  - **LRV > 4 (1 LVT) up to > 5 logs (10 LVT)**
- Budget estimate
  - Preliminary testing, mock run; spike runs & titration: ~ 50-60 k€/virus
  - 40-45 k€/additional virus

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Conclusions

- Regulatory compliance & process validation
  - No specific requirement
- Process design
  - Adaptation of batch procedures
  - CQAs unchanged
- Process control
  - Characterization & maintaining steady state operation
- Viral clearance management
  - Two main approaches:
    - Introduce sequential steps to follow standard batch procedure (pH inactivation)
    - Develop specific downstream model (virus spiking)

Thanks

Any questions ?

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