Multiproduct resin reuse (MRR) strategy in clinical development

CASSS Strategy Forum Oct 2024

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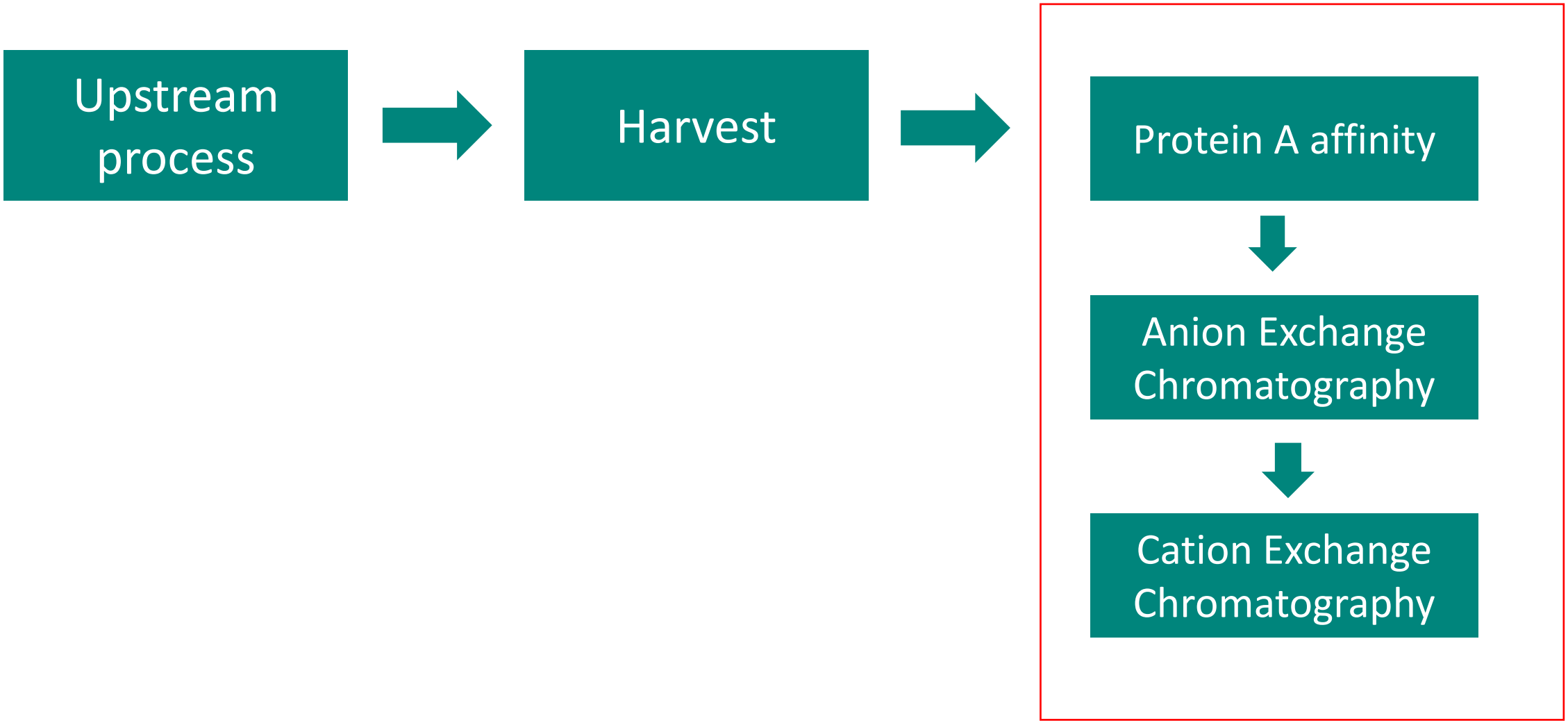
Agenda

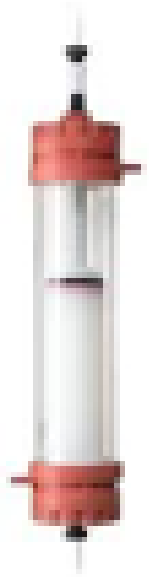
- What is MRR?
- MSD experience
- Results of cleaning studies
- Regulatory considerations

MRR principles

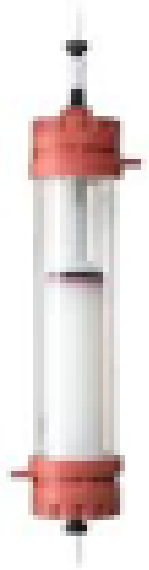
Standard Downstream Process for antibody production



Reuse of chromatography resins - standard process



Cleaning

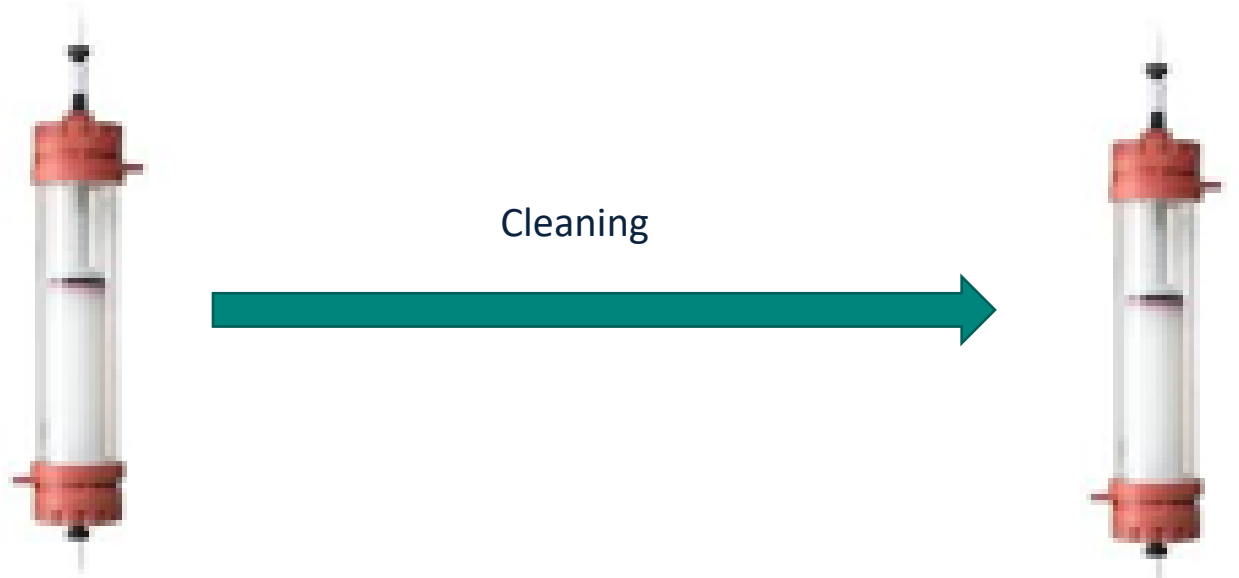


Product A
Campaign 1

Product A
Campaign 2

Re-use of resins can be done for defined numbers of cycles

Reuse of chromatography resins – for multiple products



Product A
Campaign

Product B
Campaign

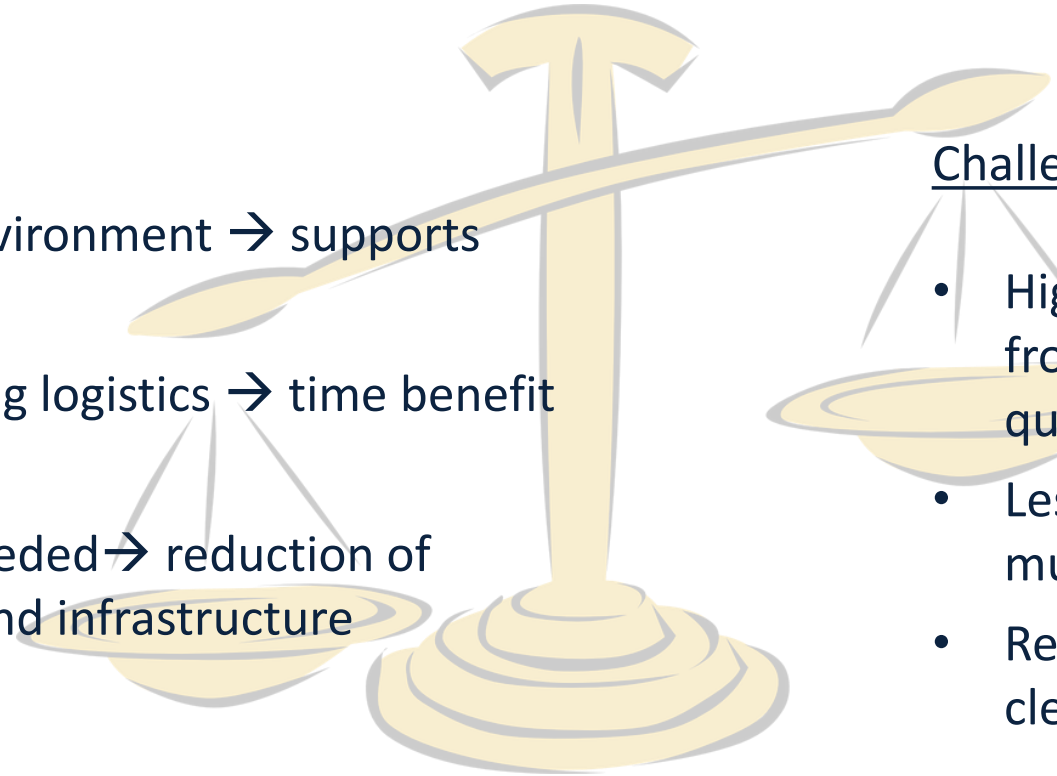
Re-use of resins can be done for defined numbers of cycles

Why use MRR strategy?

In clinical development, a resin is used only fraction of their functional life
→ Increase functional life

<u>Benefits:</u>

- Saving costs
- Positive impact on environment → supports sustainability
- Simplify manufacturing logistics → time benefit for ordering
- Less storage space needed→ reduction of complexity in utility and infrastructure

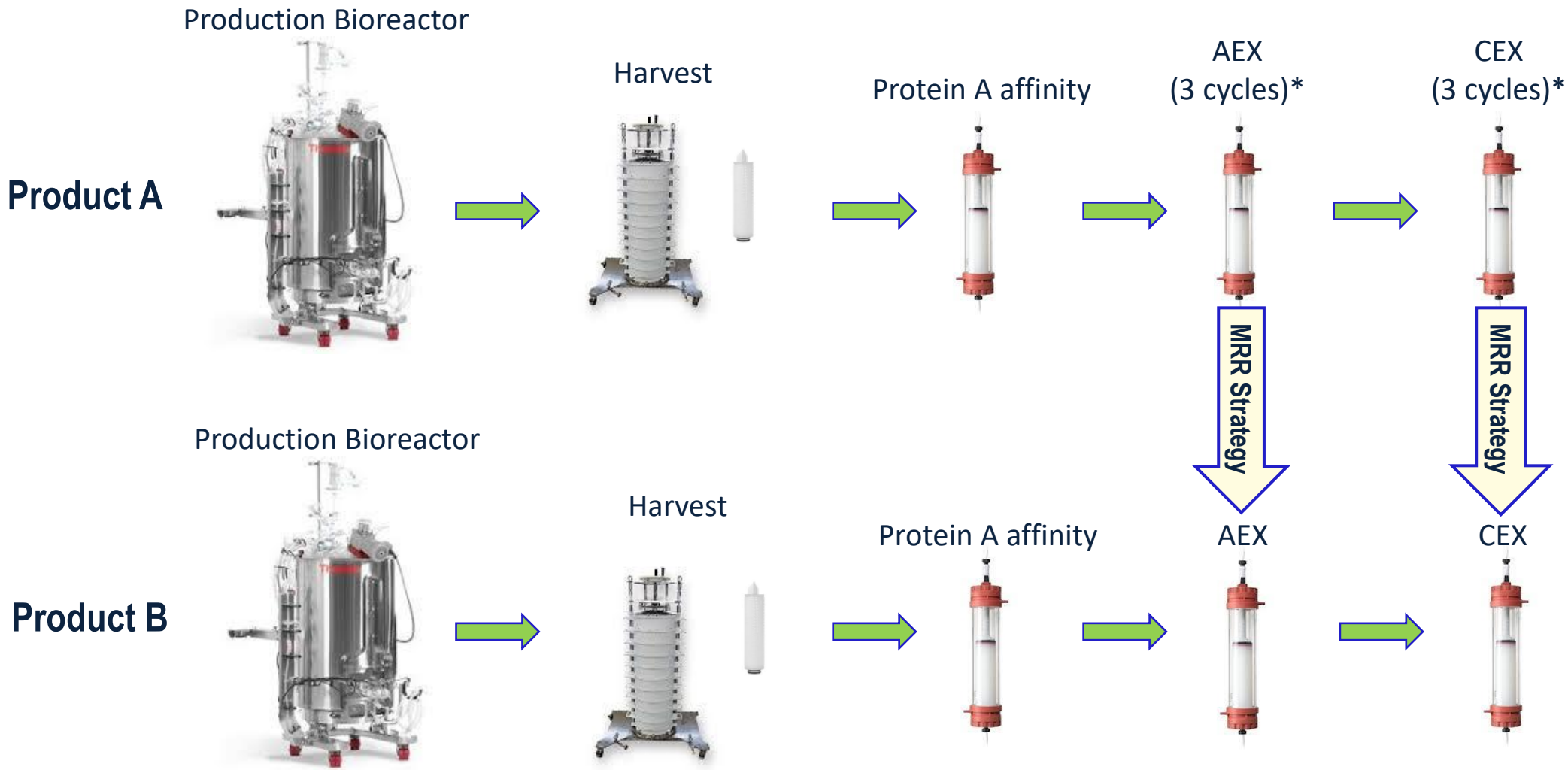


<u>Challenges:</u>

- Higher level of assurance of safety from carryover (testing and qualification)
- Less experience with (harsher) multiuse product cleaning
- Regulatory expectations are not clearly defined

MSD experience

Multiproduct Resin Reuse Strategy for Phase I GMP Manufacturing



Major questions

- Risk of potential carryover / acceptance limits
- Analytical methods for carryover detection
- Clearance procedure justification
- Regulatory acceptance?
- A generic approach?

Considerations and risk evaluation

Product safety assessment	• Whether the previous product is highly potent (indication, dosing) • Safety profile of the previous product (preclinical, clinical study results available?)
Resin Reuse compatibility assessment	• Product characteristics (pI, modality, MoA) • Manufacturing process compatibility (cell line, process; separation mechanisms between product and impurities)
Operational risk assessment	• Cleaning procedure, protein carryover acceptance criteria, method readiness • Timeline, Manufacturing site readiness

Strategy

Degradation study (without resin)

Purpose:

Confirm inactivation of Product A DS after NaOH treatment outside resins/columns

Method:

- Without involving the resins and columns.
- Incubation of Product A at certain concentration at defined concentration NaOH for certain time.

Lab scale study with resin

Purpose:

Demonstrate cleaning process and carryover clearance from defined scale

Method:

Manufacturing process at lab scale.

Cleaning protocol: Flushed with 1 M NaOH and then hold for 60 min

Performing a blank elution run after inter-campaign cleaning and prior to product changeover

Blank study done 3 times for each column

Pilot scale 200L with resin

Purpose:

Demonstrate cleaning process and carryover clearance from defined scale

Method:

Manufacturing process at defined scale. No other changes than scale.

Cleaning protocol: Flushed with 1 M NaOH and then hold for 60 min

Performing a blank elution run after inter-campaign cleaning and prior to product changeover

GMP DS run (with resin)

Purpose:

GMP manufacturing

Method:

Demonstration of cleaning process same for Pilot scale

Risk assessment with all available data done before GMP batch

Setting acceptance criteria before GMP manufacturing

Results of cleaning studies

Degradation study

1 M NaOH
Static Hold for Product A

Results confirmed by SDS-PAGE, Intact mass (LC–MS), UP-SEC, Reduced peptide mapping (LC–MS), and ELISA

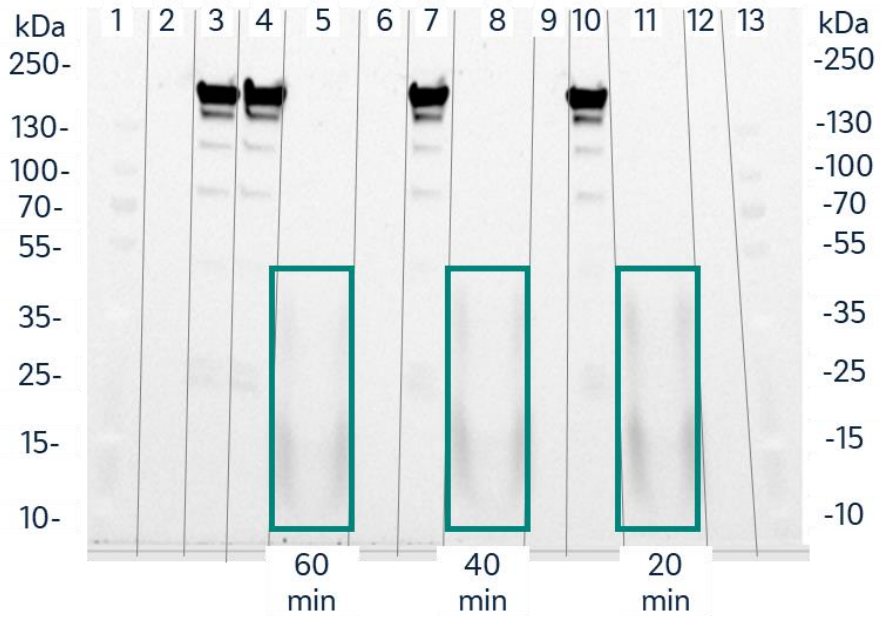
After 20 min:

→ No active protein

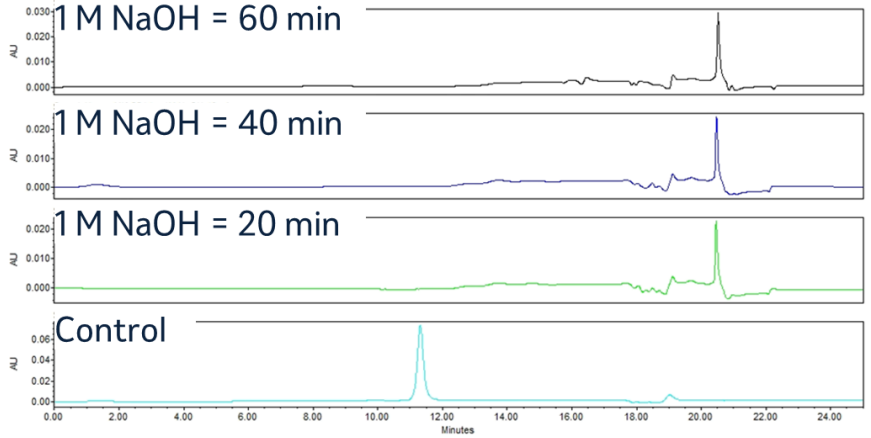
→ No total protein detected

SDS-PAGE:

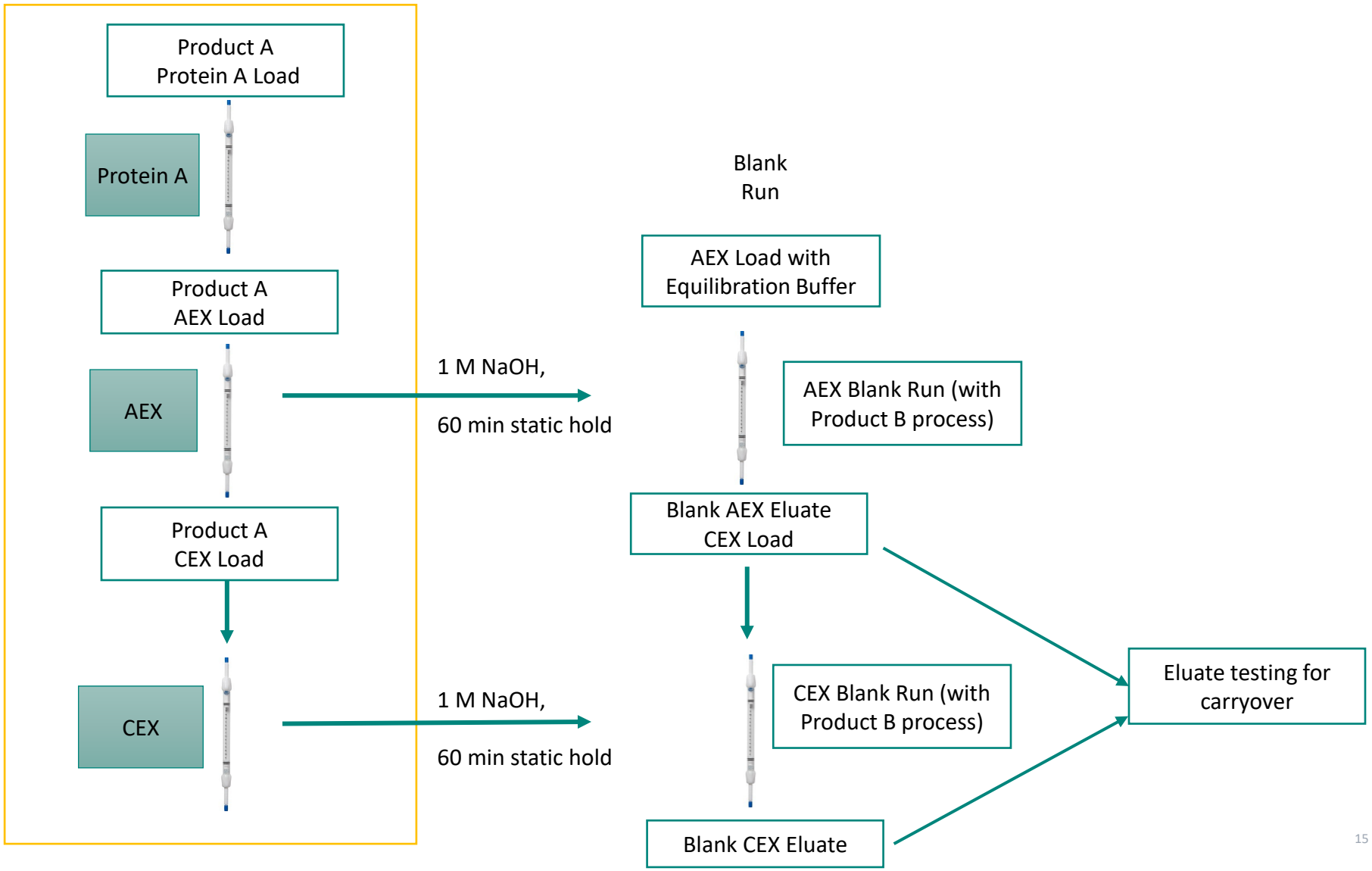
Lane 1	MWM
Lane 2	Blank
Lane 3	Protein A DS
Lane 4	Protein A Control 60 min
Lane 5	Treated w/ 1 M NaOH @60 min
Lane 6	Blank
Lane 7	Protein A DS
Lane 8	Treated w/ 1 M NaOH @40 min
Lane 9	Blank
Lane 10	Protein A DS
Lane 11	Treated w/ 1 M NaOH @20 min
Lane 12	Blank
Lane 13	MWM



UP-SEC:



Cleaning effectiveness with resins – Blank elution studies



MSD

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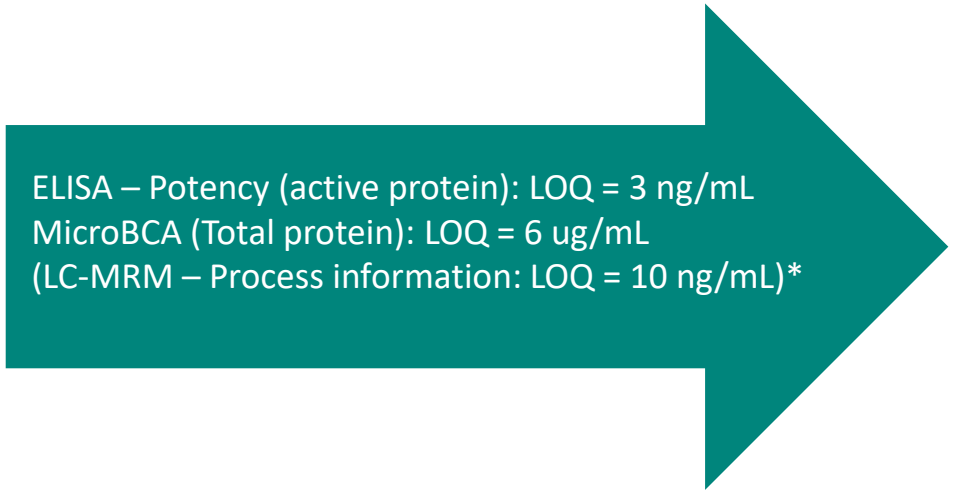
Blank elution studies

Blank elution runs following 1 M NaOH sanitization



< LOQ

Studies demonstrate cleaning with 1 M NaOH can reduce protein carryover to below LOQ
→ **Product A is sufficiently degraded and removed**

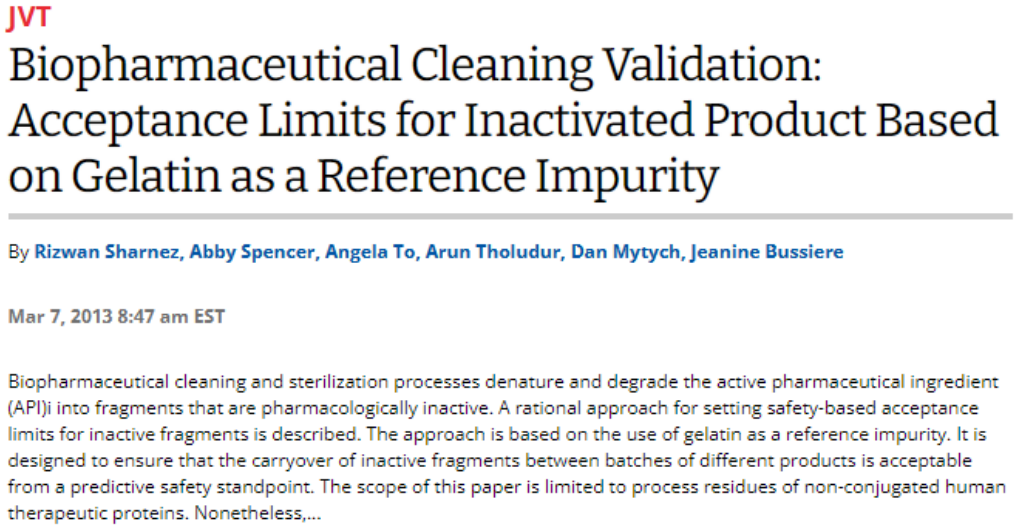
* Only lab scale and 200L scale

Setting acceptance criteria for product carryover

Protein carryover limit of 650 ug/dose

Acceptance limits for carryover based on Gelatin

- Size distribution of 15-400 kDa
- Used in medicines at 100 - 15,000 ug/dose as stabilizer
- Lupron Depot – intramuscular drug administered in multiple doses over a long period has 650 ug/dose limit



JVT

Biopharmaceutical Cleaning Validation: Acceptance Limits for Inactivated Product Based on Gelatin as a Reference Impurity

By Rizwan Sharnez, Abby Spencer, Angela To, Arun Tholudur, Dan Mytych, Jeanine Bussiere

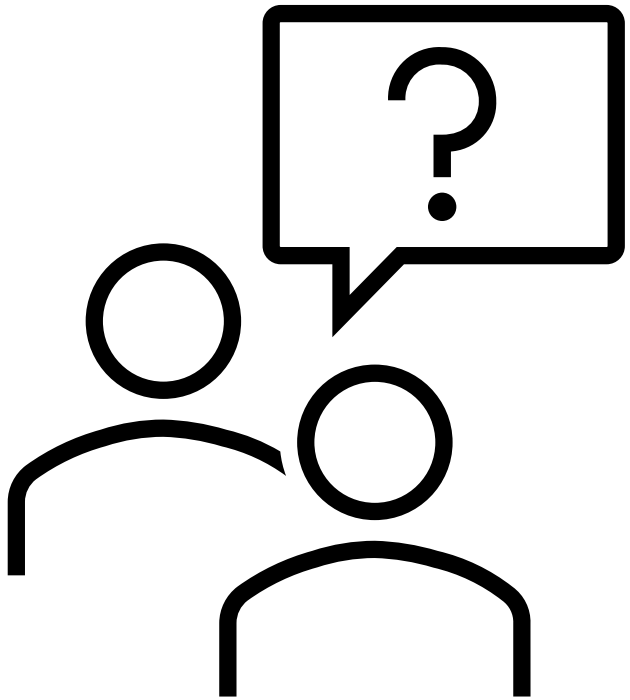
Mar 7, 2013 8:47 am EST

Biopharmaceutical cleaning and sterilization processes denature and degrade the active pharmaceutical ingredient (API)i into fragments that are pharmacologically inactive. A rational approach for setting safety-based acceptance limits for inactive fragments is described. The approach is based on the use of gelatin as a reference impurity. It is designed to ensure that the carryover of inactive fragments between batches of different products is acceptable from a predictive safety standpoint. The scope of this paper is limited to process residues of non-conjugated human therapeutic proteins. Nonetheless,...

Regulatory considerations

Questions

- Do we approach the concerned authority before submission? If so, how?
- Which details do we want to discuss with the authority?
- Do we mention MRR strategy in our dossier? If so, identify sections and related information.



Regulatory considerations cont.

Regulatory Strategy:

Authority Meeting:

- Supportive data in briefing package
- Response to comments and meeting discussion

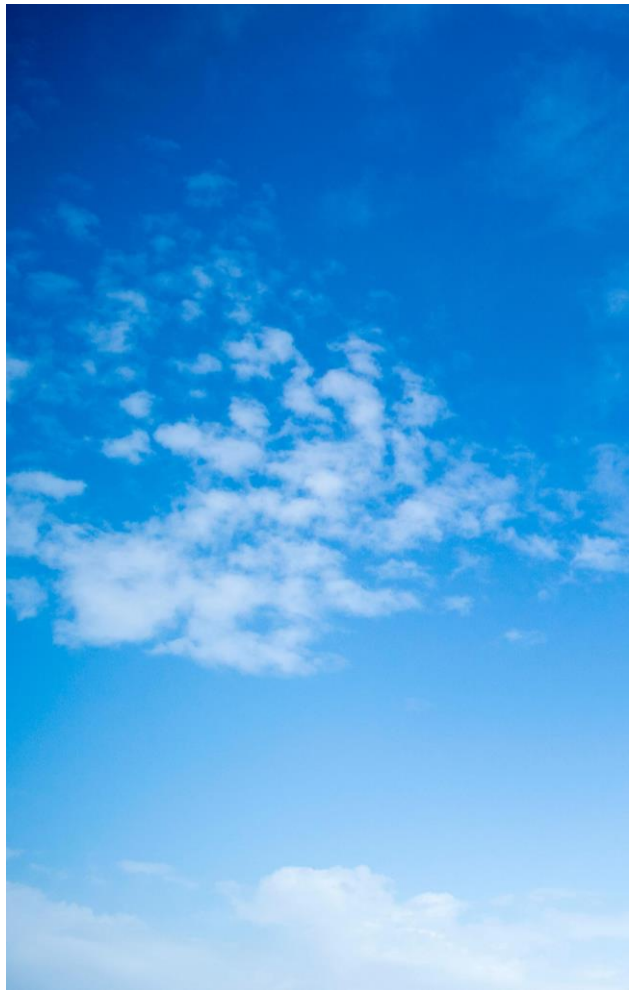
Submission:

- MRR mentioned in IND/IMPD section 3.2.S.2.6
- Separate document including risk assessment, strategy and data from studies

Conclusion

- AEX and CEX resins can be reused for multiple products using a comprehensive strategy of cleaning and product carryover pre-defined acceptance limits.
- Results show that multi-product resin reuse does not impact product quality.
- Using MRR strategy including a risk assessment, analytical development and GMP execution, multiproduct resin reuse for AEX and CEX could be utilized.

Future blue sky vision



- MRR is used on regular basis for development and commercial manufacturing
- Operation is handled according to GMP like for equipment:
  - Cleaning protocol internally available for cleaning each column (protein A, CEX, AEX). Applies to defined/all products.
  - Cleaning validation is internally available for each column and product ensuring that each column can be cleaned sufficiently.
- Resins are not dedicated to one product any more, but can be used back and forth for several products until life time is expired.
- This approach is accepted by regulatory authorities globally.

Acknowledgements

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Publication

BIOTECHNOLOGY PROGRESS

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RESEARCH ARTICLE

Bioseparations and Downstream Processing

Advancing multiproduct resin reuse for development and clinical manufacturing of an antibody-based therapeutic

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Questions? → Panel discussion

Thank you