Developing an Appropriate Design Space Strategy to Mitigate Variability in Downstream Processing Operations

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Overview

- Chromatography column scale up approach
  - Scale up considerations and challenges
- Chromatography Adsorbent Lot Variability
  - Two case studies
    - HIC- Monomer/Aggregate Separation
    - Anion Exchange-Product-related Impurity Separation
- Design Space Approach
  - Ways to control adsorbent lot variability through QBD
- Conclusions and acknowledgements
General Chromatography Column Scale Up Approach

- Bed height constant during scale up
- Scale up by increasing column diameter and volumetric flow rate
  - Development scale to cGMP scale: ~10,000x Volumetric Scale up factor
Scale Up Challenges with Adsorbent Lot Variability

• Different lots may need to be used across scales
  – Multiple lots/lot mixtures may be required to pack a large scale column

• If adsorbent lot variability exists, risk that column performance/product quality could change during scale up
Case Studies

• Case Study #1
  – HIC (Phenyl Sepharose FF) adsorbent lot variability
    • Differences in yield and aggregate removal using different adsorbent lots

• Case Study #2
  – Anion Exchange adsorbent lot variability
    • Differences in yield and removal of process-related impurity species during column wash step
Case Study #1

HIC Adsorbent Lot variability
Motivation for Study

- HIC commonly used to separate monomer and aggregate species for protein therapeutics (monoclonal antibodies, fusion proteins)

- HIC adsorbent (Phenyl Sepharose FF) – must reduce aggregate levels from 10–20% to < 1%
  - Difficult separation – Column yields limited to <70%
    - Superior adsorbent for this particular separation
  - Separation sensitive to column residence time (operating velocity, bed height) and column loading

*Column performance sensitive to adsorbent lot (ligand density)*
• Similar elution profile for lots having lower ligand densities
  – Ligand density of 40 and 42 μmole/mL $\rightarrow$ Similar elution peak profiles

• Smaller elution peaks when adsorbent ligand density was increased to 45–47 μmole/mL
  – Suggests product yield (and maybe purity) could be different when using adsorbent lots containing higher ligand densities
Potential Scale Up Challenge: Lot to lot Performance Variability

Development Data: Column yields for Different adsorbent Lots (Isocratic elution conditions)

- Downward trend of yield with higher ligand densities
  - Lot to lot variability

*Use modeling insights to evaluate impact of adsorbent lot variability prior to scale up*
Modeling to Assist in Process Scale-Up

- Formulate mechanistic model to predict Monomer/Aggregate separation over range of column operating conditions
  - Determine governing separation performance parameters
  - Predictive tool

- Understand mechanism responsible for lot-to-lot variability in performance
  - Apply model to evaluate acceptable operating conditions prior to scale up
  - Developing a “use test” to aid in adsorbent screening and potential design space prior to scale up
Adsorption of Monomer/Aggregate Species

Competitive Langmuir Isotherm model with irreversible binding of aggregate species

- Aggregate species binds irreversibly to the HIC adsorbent
  - Irreversible term included in the Adsorption Isotherm Model

\[ Q_1 \rightarrow \text{Phenyl Sepharose Adsorbent Surface (Solid Phase)} \rightarrow Q_2 \]

• Able to distinguish lots containing different ligand densities using an alternative test (Binding Constant from Adsorption isotherms)
Further Model Applications: What happens if we are not able to “Cherry Pick” adsorbent lots?

- Can we use the model to determine acceptable operating conditions if the adsorbent lot or lot mixture is outside the “acceptable” range?
• Using adsorbent lots with lower ligand density levels will increase aggregates above acceptable levels (e.g. 0.35 M Ammonium Sulfate, < 2.0% Aggregate)
Effect of Higher adsorbent Ligand Density: Experimental Data

Feed: 20 % aggregate

- Change of operating conditions will be required (increase Ammonium Sulfate concentration from 0.35 to 0.45 M)
Modeling Predictions to Guide Scale Up

- Model used to predict acceptable operating conditions
- For a ligand density of 47 μmole/mL, aggregate levels will be 2.0% and product yields 50% if Ammonium sulfate concentration in the elution buffer is 0.29 M

Feed: 20% Aggregate
• Similar product purity and yield achievable for lower ligand density lots (42 μmole/mL) if AS concentration increased from 0.29 M to 0.41 M AS
Mechanistic Modeling to Guide Process Scale up for Adsorbent Variability

- Mechanistic model provides additional insight on separation performance prior to scale up
  - Determine most sensitive (governing) input parameters
  - Useful for predicting performance of the unit operation outside the range explored during development
  - Developed a protein-specific use test to assist in screening adsorbent lots

- Model applied to predict acceptable conditions for different adsorbent ligand density levels
  - Useful if selection of adsorbent lots with specific ligand densities is not possible
Model Case Study #2

Anion Exchange Adsorbent Lot variability
Background for Case Study #2

• Anion exchange column performed in the “bind/elute” mode
• Main function of column
  – Removal of a product-related impurity species in wash step (prior to product elution)
    • Desirable to have 5-10% product loss in wash to ensure the product-related impurity is effectively removed
• Difficult separation due to similarities between the product-related impurities and target product
  – Column performance sensitive to changes in column loading and wash buffer composition (pH, Osmolality)
• Significant adsorbent lot variability
• Increase in protein loss during wash step for adsorbents lots containing higher Ionic Capacity
  – Some resin lots which did not follow the trend

\(^1\)Cecchini, D.; *Quality by Design for Biopharmaceuticals*, 2009, P. 140
• Increase in protein loss during wash step for adsorbents lots containing higher Ionic Capacity
  – Some resin lots which did not follow the trend
• May require an additional correlation beyond one provided on the COA or by the Vendor

1Cecchini, D.; Quality by Design for Biopharmaceuticals, 2009, P. 140
Lot to lot variability measured during protein adsorption isotherm experiments using the wash buffer conditions.

- Measure the binding constant ($K_L$) for each of the adsorbent lots.

adsorbent ionic capacity

- 99 μeq/mL
- 153 μeq/mL
- 131 μeq/mL

$q = K_L \times C$
Correlation between Protein Loss (in Wash step) and Binding Constant for different Adsorbent Lots

- Correlation between binding constant and column performance
  - Process-specific use test can be used to detect differences in adsorbent lot performance
How do we control differences in lot variability during GMP MFG?
  - Potential impacts on both process consistency and product quality

Several Approaches Exist
  - Conventional Approach
    - Select operating conditions/range in which all adsorbent lots will have acceptable performance
    - May result in sub-optimal process performance
  - “Cherry pick” Approach
    - Use only certain adsorbent lots in MFG processing
    - May or may not be possible
    - Not desirable
  - Design Space/QBD Approach
    - Design space filing which includes ranges in column operating conditions
    - Can control adsorbent lot variability through changes in the column operating conditions
Design Space Approach for Anion Exchange

Effect of Wash Buffer pH and NaCl Concentration on Product Loss in Wash

- Change the wash buffer composition to achieve the appropriate level of product removal during the wash step
- Provides flexibility in managing different adsorbent lots
  - Potential impacts on both process consistency and product quality

Adsorbent Lot “A”
Design Space Approach for HIC

- Change the Elution Buffer Ammonium Sulfate concentration to achieve consistent product quality and yield for different adsorbent lots

Feed: 20% Aggregate
• QBD filing can include ranges for elution buffer composition
  – Selection of the elution buffer composition can be based upon the adsorbent lot binding constant
• Provides additional process control to ensure consistent and optimal process performance
Conclusions

• Adsorbent lot variability should be evaluated, especially when performing difficult separations
  – Illustrated with two case studies: HIC and Anion Exchange columns
  – Formulated a mechanistic model useful as a predictive tool

• Adsorbent CoA information can be helpful, but a process/product specific use test may be required to correlate adsorbent lot variability with process performance
  – Measurement of adsorption isotherm binding constants-useful to detect difference among adsorbent lots

• Flexibility in selecting elution or wash buffer composition to provide optimal process performance
  – Design Space/QBD Filing strategy could be used to implement this approach in drug substance manufacturing
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References

• Phenyl Sepharose Modeling and Adsorbent Lot variability across scales