Recommendations for Protein A Chromatography Techniques and Processes in Clinical Trials

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I. Background

KBI Biopharma

A contract development and manufacturing organization (CDMO) with multiple sites in the Research Triangle Park. The company specializes in development of upstream and downstream processes to meet client goals of pharmaceutical drug clinical development or manufacture.

Project Motivation

Goals

To compare different combinations of Protein A Chromatography methods through both a productivity and economic lens assuming a 2000 L cGMP biomanufacturing plant for a CDMO performing Phase I clinical trials on behalf of their customers.

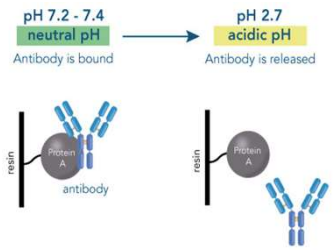
Deliverables

1. Literature Review
2. Productivity Analysis
3. Economic Analysis
4. Productivity and Cost Analysis Tool

II. Introduction

Protein A Chromatography

A robust and common method of monoclonal antibody (mAb) capture used in development and manufacture. This type of chromatography is affinity based as it takes advantage of the binding specificity of the immobilized protein A ligand for antibodies while rejecting other impurities.

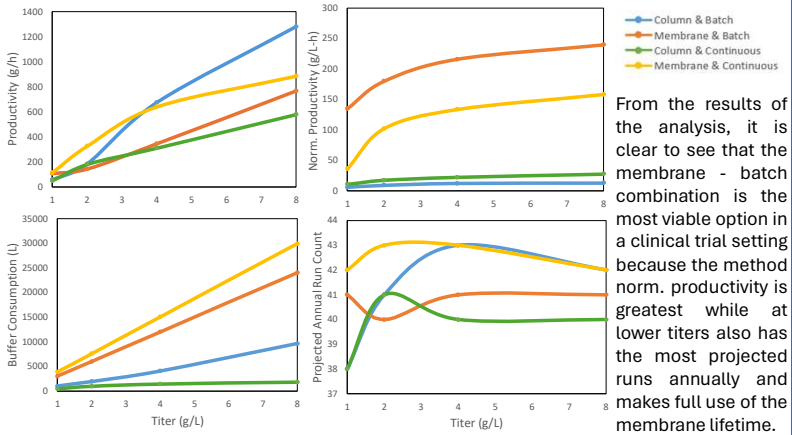


Combinations

Purification can be carried out in batch or continuous mode utilizing resin or membranes for mAb capture. Each combination comes with a set of advantages and disadvantages which were analyzed in this project and then extrapolated to arrive a decisive conclusion on which method would be most profitable in the setting of GMP clinical trials.

III. Productivity Analysis

An analysis of the productivity of the Protein A capture step was developed by using design parameters defined by KBI in conjunction with other necessary parameters found in the literature review. Among many key results and defining process parameters, the most important are productivity, normalized productivity, buffer consumption, and projected annual run count, shown in the figures below.



From the results of the analysis, it is clear to see that the membrane - batch combination is the most viable option in a clinical trial setting because the method norm. productivity is greatest while at lower titers also has the most projected runs annually and makes full use of the membrane lifetime.

IV. Economic Analysis

The economic analysis investigated two different types of cost for protein A chromatography: capital and operational cost. The capital cost, found in Figure A, concluded that batch processing equipment cost half as much as continuous processing equipment. In order to analyze the operational cost, it was tabulated at different levels of scope to ensure the depiction of the most cost-effective combination. The first scope was looking at the operational cost of a single run which is found in Figure B. The second examination was the annual operating cost in Figure C. In Figure D, the annual operating cost was normalized by annual product production. All of the operational cost calculations demonstrated that batch-membrane is the most cost-effective combination for KBI Biopharma clinical trial manufacturing.

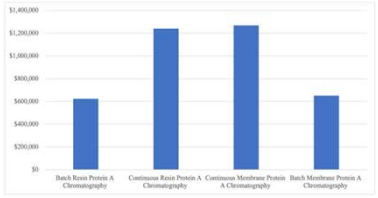


Figure A. Capital Cost of Protein A Chromatography Combinations

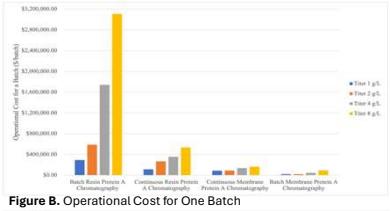


Figure B. Operational Cost for One Batch

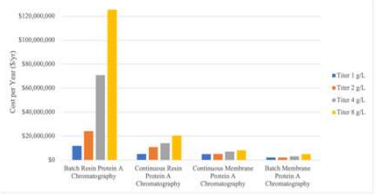


Figure C. Annual Operational Cost

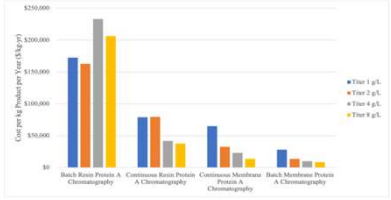


Figure D. Annual Operational Cost per Product Production

V. Productivity and Cost Analysis Tool

Using information found during the literature review and data provided by the KBI team, a productivity and cost analysis tool was created to facilitate calculations for hypothetical processes by implementing a compilation of inputs and outputs for all four methods, creating a central hub for making quick alterations to process parameters and reviewing results for both productivity and associated costs.

Please refer to the screen for a display of this tool at work!

VI. Conclusion

After a thorough analysis of the data, the team recommends that the membrane batch combination be implemented for clinical manufacturing. A membrane batch process has the lowest annual operating cost, lowest annual operating cost per product produced, second lowest associated capital costs, highest productivity when normalized, and the highest number of batches per year.

	Column & Batch Process	Membrane & Batch Process	Difference
Capital Costs	$ 622,600.00	$ 650,260.00	$ -27,660.00
Average Annual Operating Cost	$ 58,602,007.78	$ 3,076,269.52	$ 54,985,740.20
Average Annual Operating Cost per kg Product	$ 193,687.92	$ 14,967.69	$ 178,720.23

Next steps for this project include the purchase of the membrane and membrane holder which are needed for operation of the membrane and batch combination. There will be no additional personnel needed for this transition. The only requirements would be updated training for the adjusted standard operating procedures and current operators.

The team suggests that further testing should be done with the combination to further determine the actual productivity to ensure that it verifies what was predicted by this model.

Further research and testing is also recommended to determine how membrane-batch compares to resin columns for commercial manufacturing which are expected to have multiple runs as opposed to the clinical trial case that was considered in this project.

VII. Acknowledgements & References

Thank you to N.C. State Department of Chemical Engineering and KBI Biopharma for sponsoring this project. We would like to extend a special thank you to Thomas Lindsey, Dr. Yong Yow, and Dr. Lisa Bullard for their perpetual support and mentorship throughout the duration of the project. Please find a list of refences by scanning the QR code here: