Recommendations for an Intensified Monoclonal Antibody Manufacturing Process

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1. BACKGROUND

Project Motivation
- The biopharmaceutical industry is rapidly growing with many companies interested in improving production capabilities to meet speed to market and cost efficiency goals.

KBI Biopharma
- Contract development and manufacturing organization (CDMO)
- Durham, NC locations focused on the production of monoclonal antibodies (mAbs) with Chinese Hamster Ovary (CHO) cell lines.

Process Intensification
- Process intensification aims to improve overall manufacturing efficiency by increasing the seeding density of the production culture.
- Requires higher cell densities at the N-1 stage than traditional, low-density processes

2. INTRODUCTION

Goals
- Recommend a versatile process intensification approach that can be applied to a 2000 L cGMP biomanufacturing plant
- Determine technical and economic feasibility of the recommended process

Deliverables
- PFD of recommended process
- Technical specifications for process
- Economic analysis of intensification approaches

Perfusion Technology
- Perfusion is a mode of continuous bioreactor operation that retains cells through filtration
- Allows for extreme cell densities to be achieved
- Use at the N-1 stage could improve seed train efficiency

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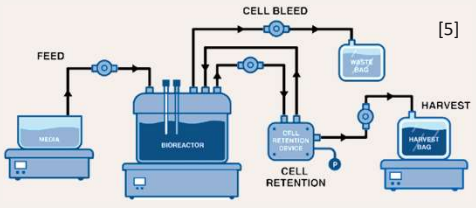


3. LEVELS OF INTENSIFICATION

Increasing N-1 Cell Density

Low Density Fed Batch (LDFB)

Vial Thaw & Shake Flask Expansion → 50L Wave Bag N-3 → 200L Batch N-2 → 500L Batch N-1 → 2000L Fed-Batch Production
SD: 0.3 x 10^6 cells/mL

High Density Fed Batch (HDFB)

Vial Thaw & Shake Flask Expansion → 20L Wave Bag N-3 → 50L Wave Bag N-2 → 500L Enriched Batch N-1 → 2000L Fed-Batch Production
SD: 5 x 10^6 cells/mL

High Density Fed Batch With N-1 Perfusion

Vial Thaw & Shake Flask Expansion → 20L Wave Bag N-3 → 50L Wave Bag N-2 → 500L Perfusion N-1 → 2 x 2000L Fed-Batch Production
SD: 5 x 10^6 cells/mL

4. RECOMMENDED PROCESS

Manufacturing Performance Comparison

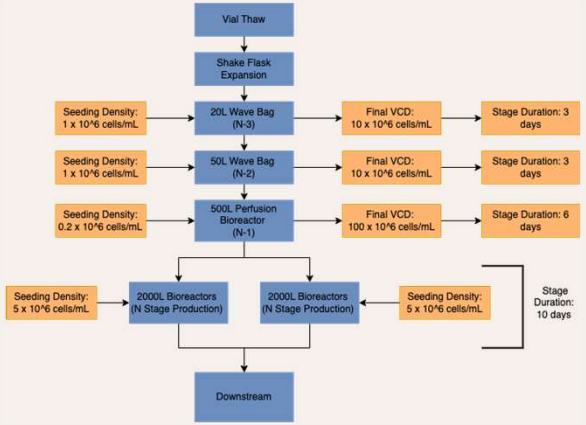
Process Type	Expected Product Yield (g/batch)*	Annual Capacity (batches/year)
Traditional LDFB	10040	20
HDFB	10040	38
HDFB with N-1 Perfusion	10040	76

*Batch refers to each 2000L production cell culture

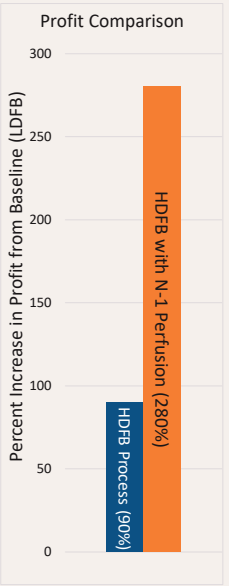
Suggested Production Culture Parameters

Parameter	Recommended Value
Viability Target for Harvest	70%
pH Setpoint	7.1
DO% Setpoint	60%
Daily Glucose Target	5 g/L
Initial Temperature	36.5°C
Temperature Shift Target	32°C on Day 5
Media Additives	Butyric Acid, Nucleoside, Lysine, Threonine, Tyrosine

- ★ Based on our comparison of each level of intensification, **we recommend a High Density Fed Batch Process with N-1 Perfusion**
- ★ Our proposed process will result in a production stage culture that achieves comparable product titer to a LDFB process, but with shorter duration batches
- ★ If N-1 Perfusion is deemed not feasible to implement, our proposed parameters can be applied to a HDFB process with an enriched batch seed



5. ECONOMIC COMPARISON



Profitability Analysis Inputs
- Depreciation: Assumes a 6-year lifetime of the capital investment by considering salvage value and the yearly depreciation allowance
- Tax Rate: 45%
- Assumptions: An existing facility is available, 70% yield from harvest to drug product, and all product is sold

Economic Conclusions
- Revenue: Highest for HDFB with N-1 Perfusion
- Capital Costs: Comparable between LDFB and HDFB. Highest for HDFB with N-1 Perfusion
- Cost of Manufacturing: Significantly higher for HDFB with N-1 Perfusion
- **HDFB with N-1 Perfusion is most profitable**

Approximate Cost (Annual Basis)	Traditional LDFB	HDFB	HDFB with N-1 Perfusion
Revenue	$9,000,000,000	$17,000,000,000	$35,000,000,000
Capital Cost	$2,400,000	$2,400,000	$3,900,000
Waste Treatment	$68,000	$93,000	$480,000
Operating Labor	$425,000	$425,000	$425,000
Raw Materials	$8,000,000	$11,000,000	$42,000,000
Utilities	$26,000	$33,000	$106,000
COM_d	$11,500,000	$15,500,000	$54,000,000
Net Profit	$5,000,000,000	$10,000,000,000	$19,000,000,000

6. CONCLUSIONS

We recommend the KBI team follow **a reduced duration HDFB with N-1 Perfusion** approach to process intensification. This provides the greatest amount of **profit, productivity, and total product output** while **increasing speed to market.**

7. ACKNOWLEDGEMENTS & REFERENCES

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Please scan me for the list of references used! -->