Breaking the $40 per gram barrier for mAbs with fully-connected continuous manufacturing (FCCM)

Himanshu Gadgil, PhD

Chief Executive Officer, Enzene

Passion. Innovation. Life.

Who we are

Enzene is an innovation-driven, technology-led differentiated biotech company offering integrated CDMO services for Biologics

Enzene, a subsidiary of **Alkem Laboratories Ltd.** and **VC-backed firm**, offers **fully integrated platform** from **Cell Line Development to Fill & Finish** across wide range of modalities.

We operate state-of-the-art **R&D facility** with Ambr 250 bioreactor and 8 more bioreactors[2] (2L-10L) and **cGMP manufacturing facilities** with 5 suites (20L-2000L) across fed-batch, semi-continuous & patented **fully-connected continuous manufacturing, EnzeneX™ (among first movers globally).** We have a **GMP facility** with supporting labs coming up in **US** (54,000 sq. ft.) by Q1 2025.

We have a robust track record of delivering **over 30 projects at different stages** from **cell line development to commercial**[1], at an **accelerated pace** (Gene to Phase 1 within ~**10 months for complex proteins**)

Our **technical expertise, flexibility and tailor-made solutions,** regardless of project scope or scale, **makes outsourcing easy**

1. 6 CLD (India), 1 CLD (Global), 2 PD (Global), 2 Pre-clinical (Global), 1 Pre-clinical (India), 6 Phase 1 (Global), 2 Phase 1 (India), 3 Phase 3 (India), 1 Phase 3 (Global), 7 Commercial (India)
2. 2 additional bioreactor orders have been placed; Delivery expected by Apr'23

Key milestones: Understanding our growth as a company

2015 - 2018

- R&D and manufacturing facilities established in Pune, India
- Approvals: 7 pre-clinical and 3 clinical trials
- Established pilot plant for clinical manufacturing

2019 - 2020

- Developed and patented our fully connected continuous manufacturing platform, EnzeneX™ and established our GMP facility
- Established *E. coli* and mammalian GMP certification
- Approvals: 3 clinical trials

2021 - 2023

- Biosimilars commercialization: Romiplostim, Teriparatide, Denosumab, Adalimumab, Cetuximab, Bevacizumab and Ranibizumab
- Installed 2000L of clinical and commercial manufacturing capacity
- Delivered biosimilars for 4 Phase I clinical trials

What's next?

- US commercial GMP facility
- Increasing clinical and commercial manufacturing capacity
- Global biosimilars expansion

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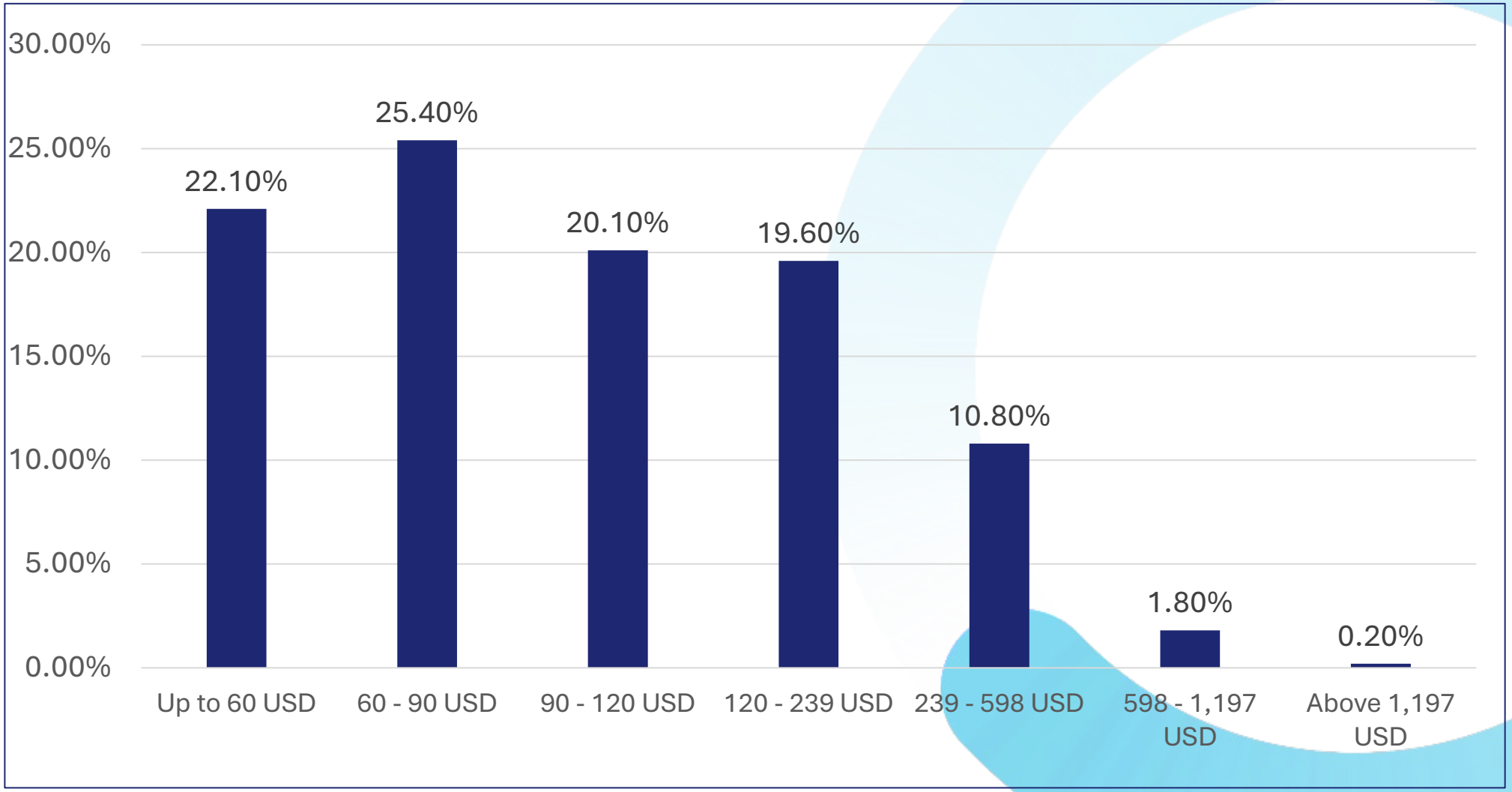
Blank Slate

http://dietplanreviews.info/goog/blank-slate.html
http://www.investinganswers.com/financial-dictionary/stock-valuation/cost-capital-112

Distribution of average monthly income in households across India in 2015



Average cost of cancer therapy is 10,000 USD

https://www.statista.com/statistics/653897/average-monthly-household-income-india/

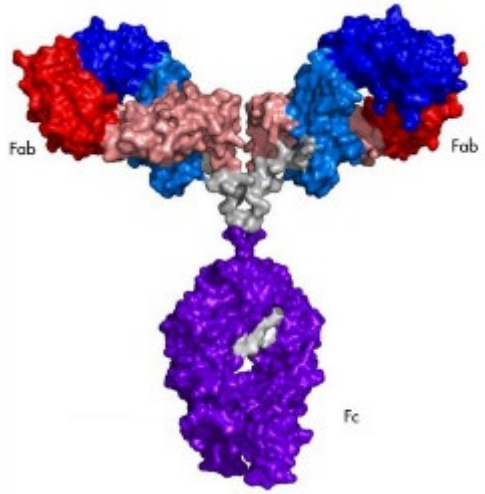
The affordability challenge in India

$ 80

Cost of Gold per Gram

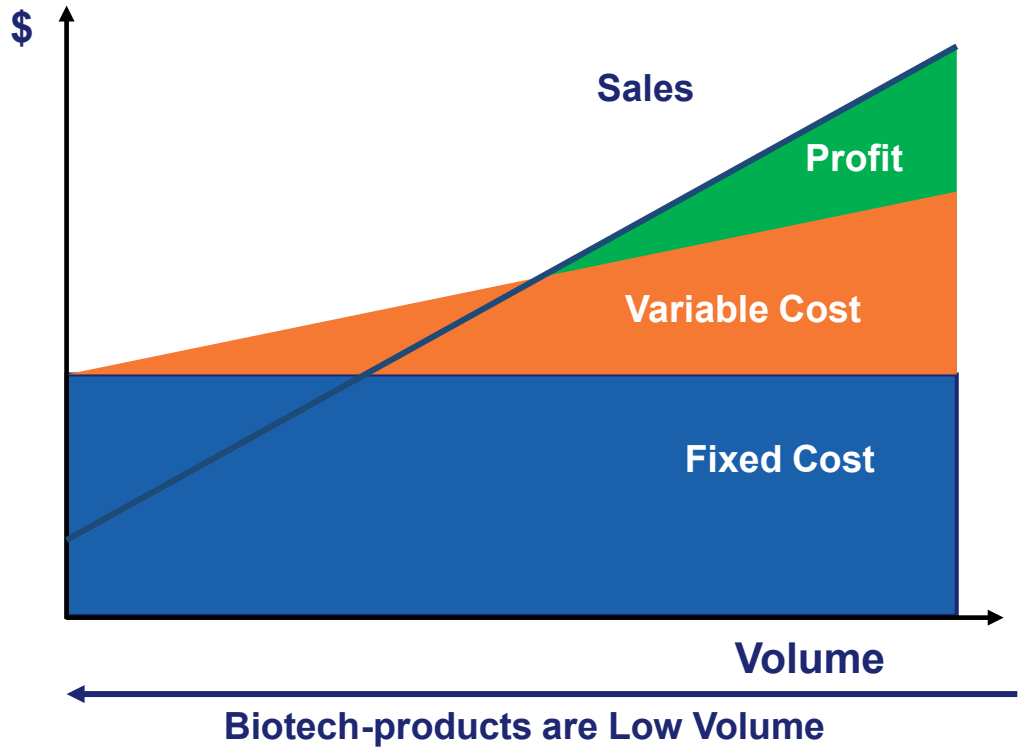
$ 150 - $500

Cost of mAb production per Gram



Cost of Capital : P&L

Profitability

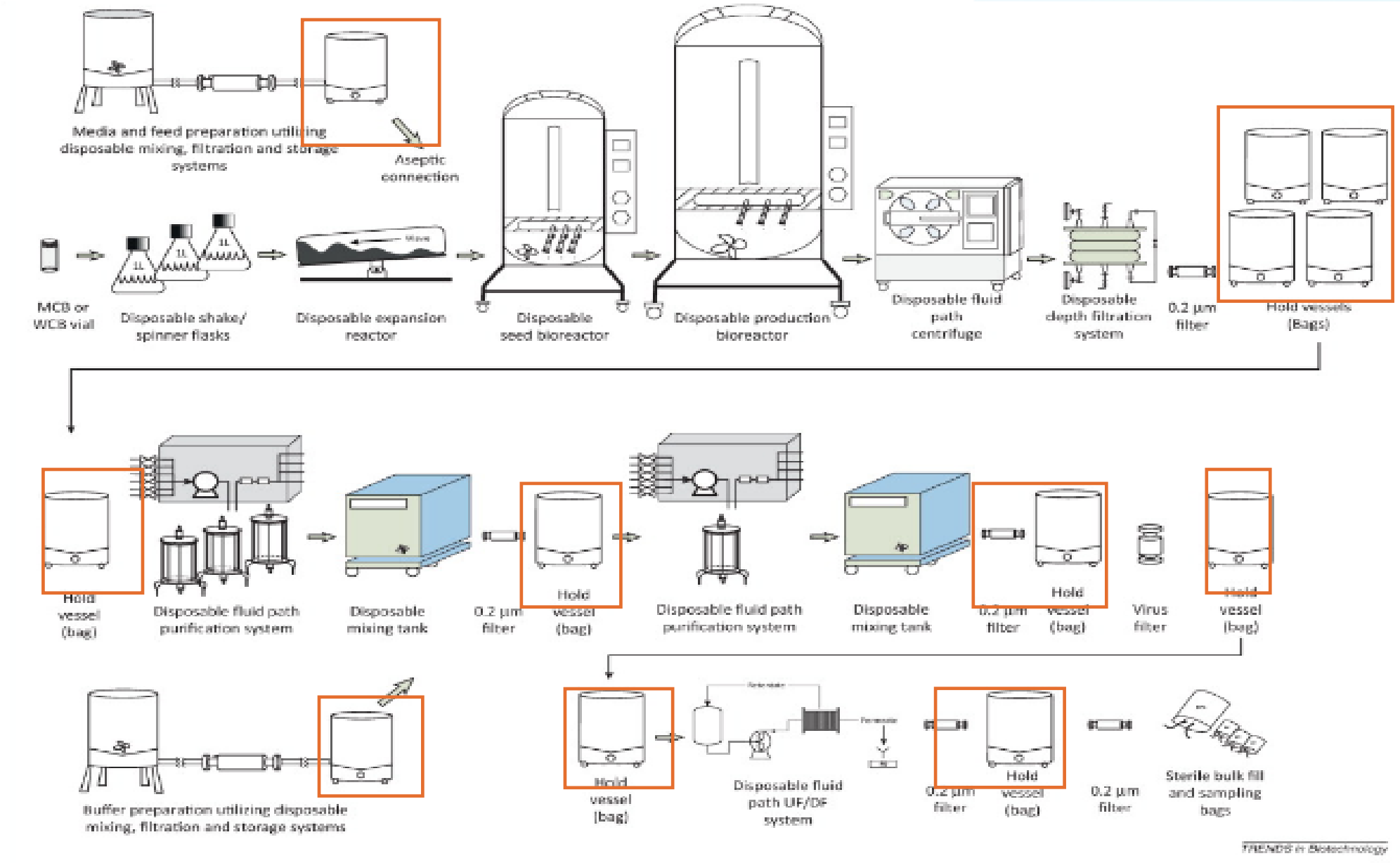


Key Contributors: Fixed Cost

- Utilities
- Maintenance
- Salary
- Amortization
- Depreciation

Can contribute up-to 50 to 60% of the fixed cost especially for new plants

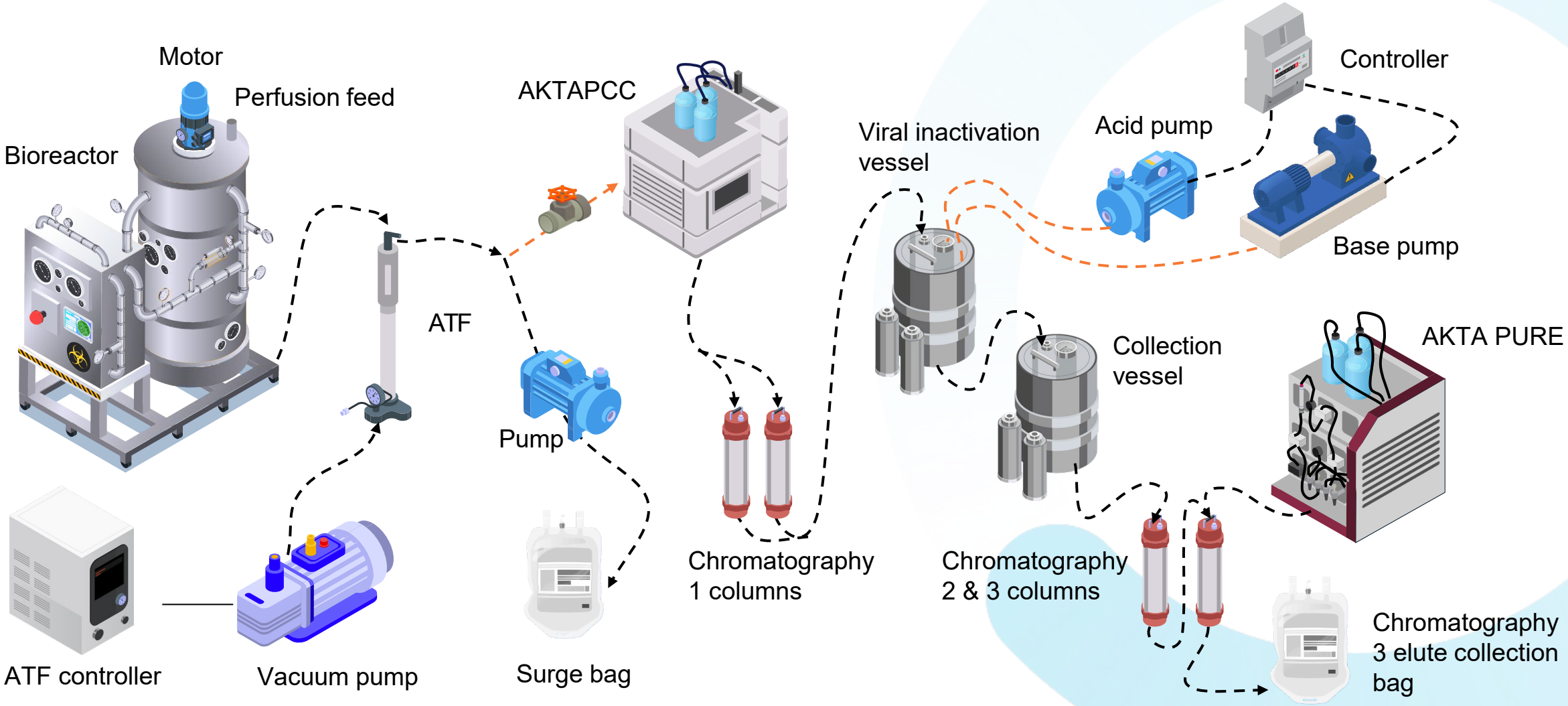
Fed-batch plants are clunky and occupy large facility footprint



Abhinav A. Shukla Uwe Gottschalk Trends in Biotechnology Volume 31, Issue 3, p147–154, March 2013

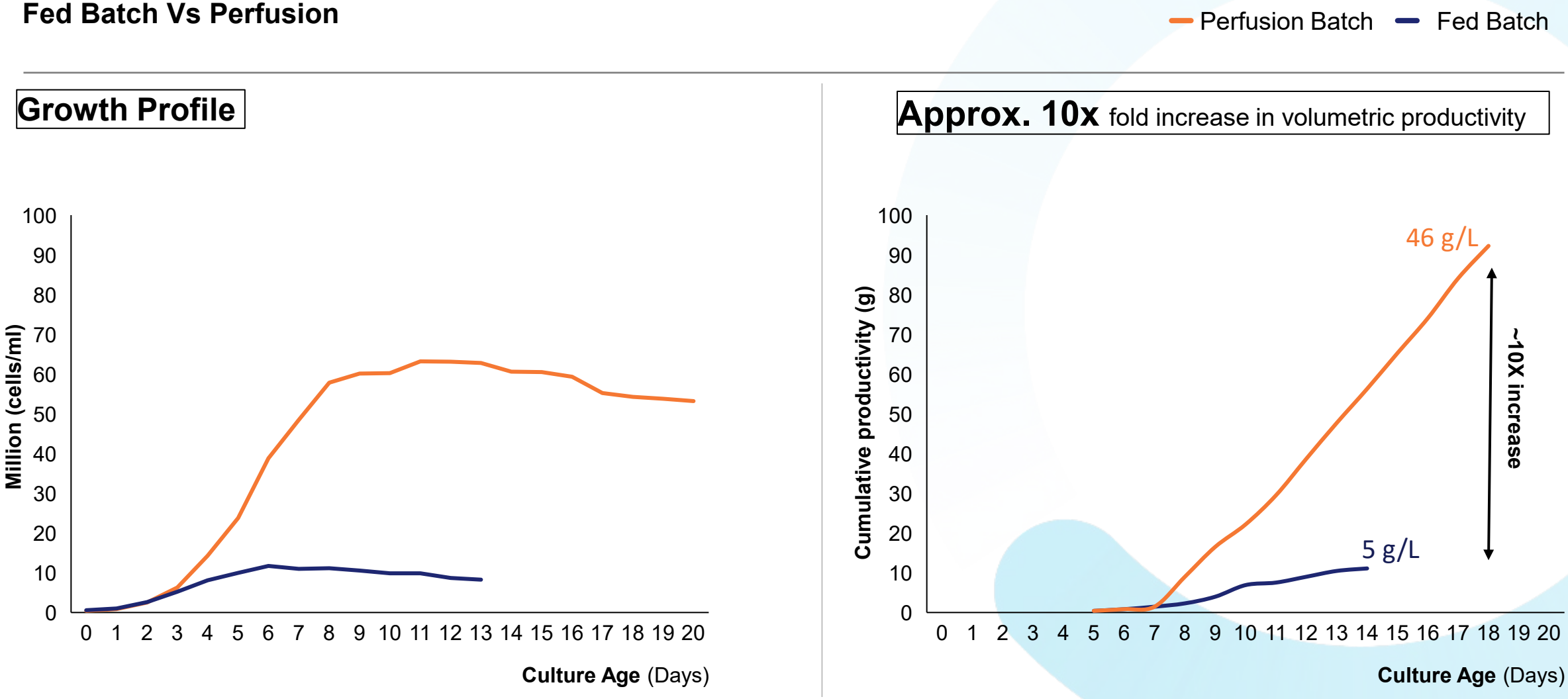
Fully-connected continuous manufacturing (FCCM)

The process behind our fully-connected continuous platform (FCCM)



Increased Productivity

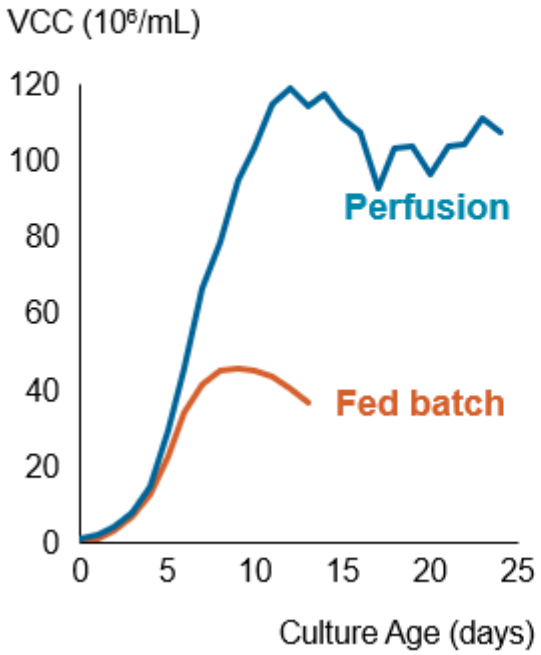
Fed Batch Vs Perfusion



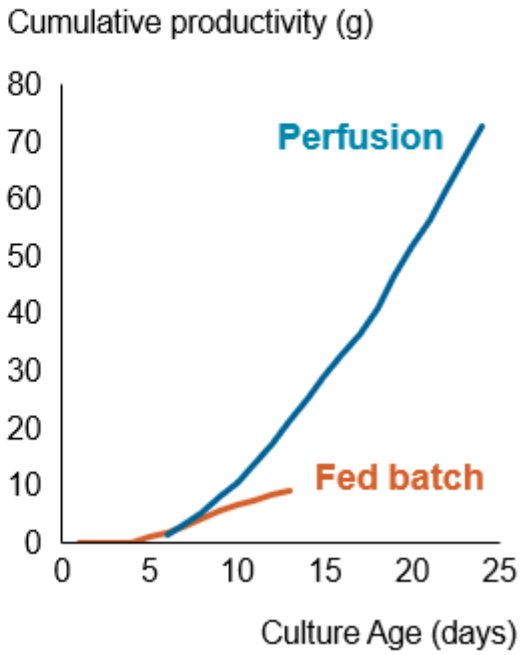
FCCM delivers ~10X higher productivity and up to 80% lower production costs

Upstream Productivity

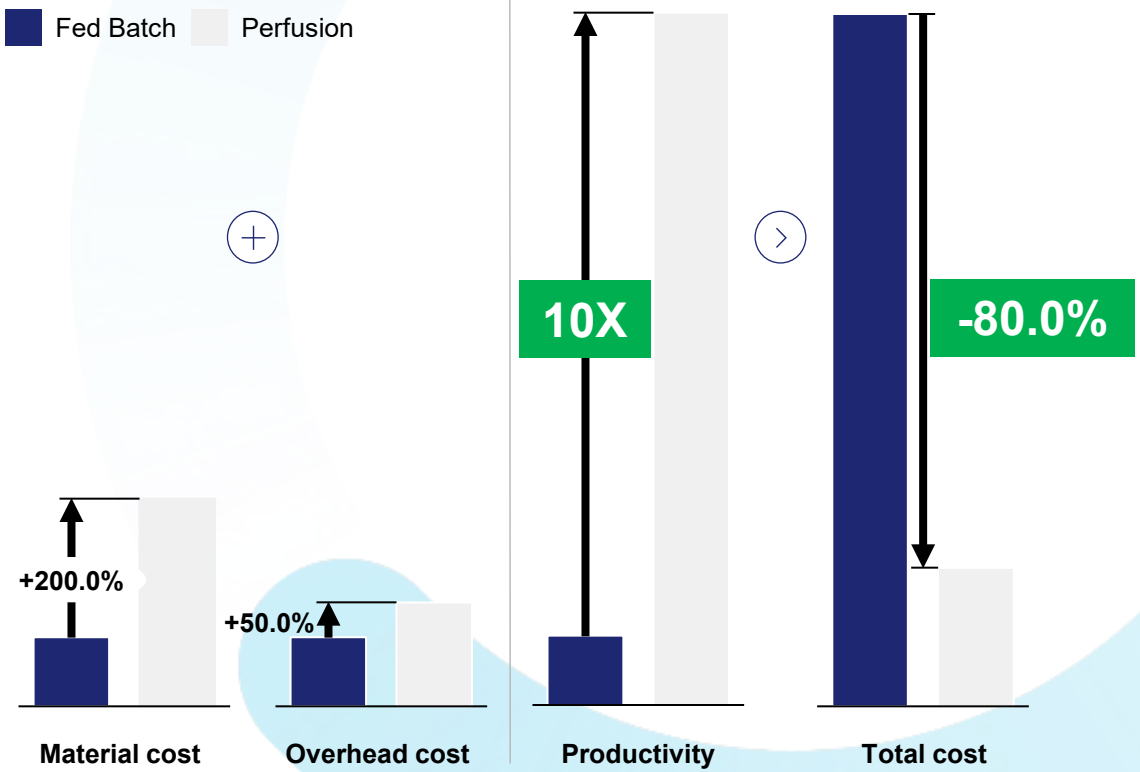
Improvement in cell growth profile



Significantly improved cumulative Productivity



~80% lower overall cost in continuous manufacturing compared to Fed batch



1. In continuous process compared to fed-batch in 2L bio-reactor

FCCM for unstable molecules

Case study: Converting fed-batch to FCCM for a complex bispecific

Challenges

Fed batch process

Poor Viability in Fed batch after day 10

Proteolytic Clipping of the molecule during manufacturing (upstream and downstream)

Limited operational pH range

Absence of a true capture step for the molecule

Heparin affinity: low recovery and leachability, expensive reagent

Continuous Process Approach

Core Drivers for continuous manufacturing

Development of a capture step

High volumetric productivity coupled with high p/c/d

Minimal product exposure to proteolytic enzymes in bioreactor and downstream unit operations

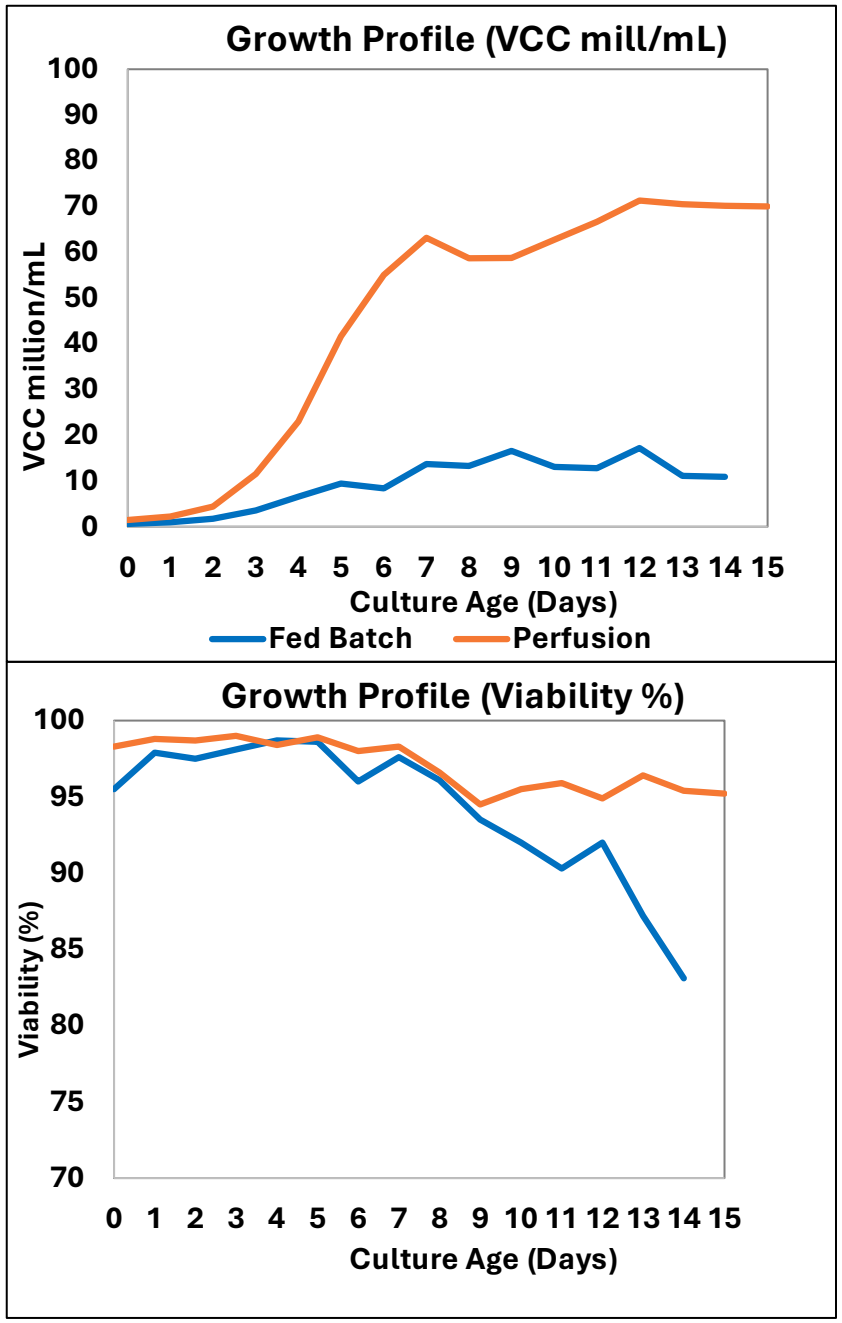
3 Major Factors determined during perfusion process development:

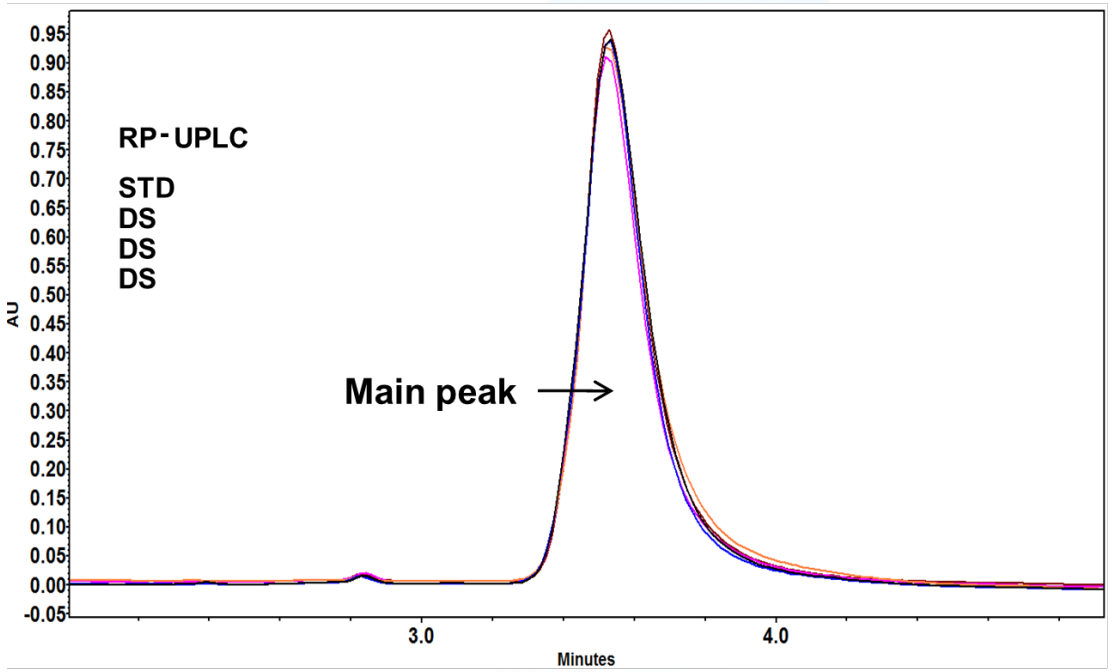
Media and Feed

Cell-specific perfusion rate (CSPR)

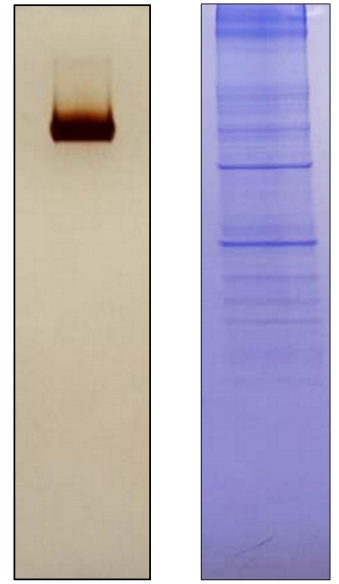
ATF exchange rate (Perfusion Rate)

Perfusion leads to substantial increase in VCC, viability & product quality





15 Day 20L Continuous process resulted in *27 gm* grams Drug substance.



ENZ process Fed batch

Rapid reversed-phase method development for daily in-process testing

Key Impact of EnzeneX™ in this case study

27 grams high quality, purified protein via 20L perfusion process (Vs 3 gram in 50L Fed-Batch)

Commercially viable manufacturing process development and cGMP technology transfer within **6 months**

Batch to batch **consistency** and **scalability** from bench to commercial

Yield > **500,000 doses** of Drug Product via 20L perfusion process

It not only allows for substantially lower protein production costs, but also lowers carbon footprint

Enzene X™ process has higher cost in terms of:

- Material costs
  (mainly media and buffer)
- Operating costs
  (suite and personnel – due to longer batch run time)

These higher costs are fully offset by superior protein productivity per batch in fully connected continuous manufacturing compared to fed-batch process

Typically, we observe 40% to 80% lower production cost with EnzeneX™ in fully connected continuous manufacturing (FCCM) compared to traditional fed batch processes at the same scale

EnzeneX™ reduces the carbon footprint by up to 50%, compared to traditional fed-batch processes

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The value of using FCCM

Increased productivity

~10x upstream and 25-50% downstream

Cost-effective manufacturing

40 – 50% reduction in processing costs

Quality manufacturing

For sensitive and complex biologics, including fusion proteins and bispecific antibodies

Flexibility and product scaling

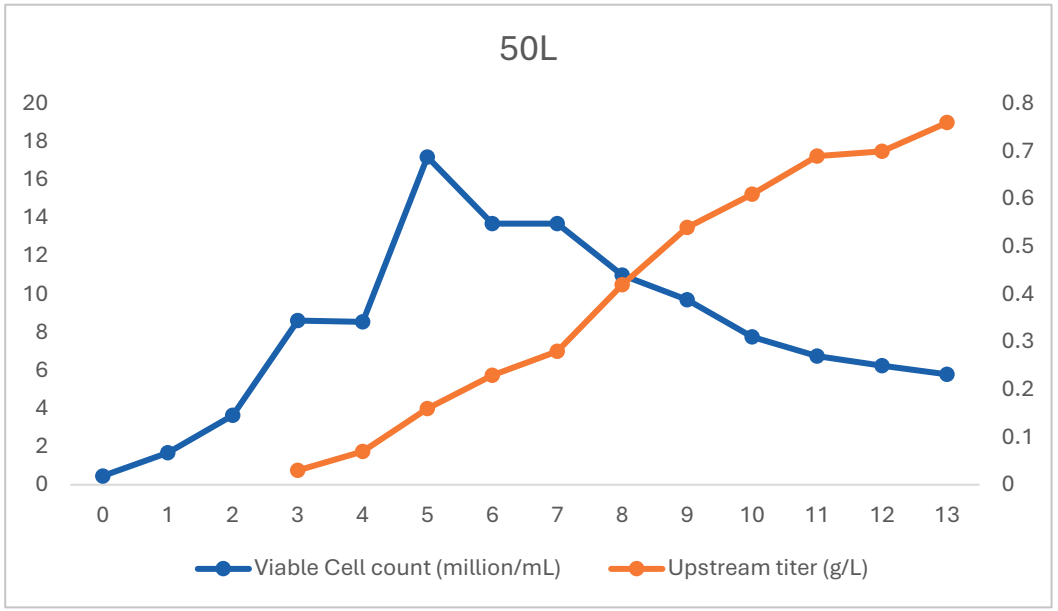
Variable bioreactor capacity with scale-on and scale-out approach

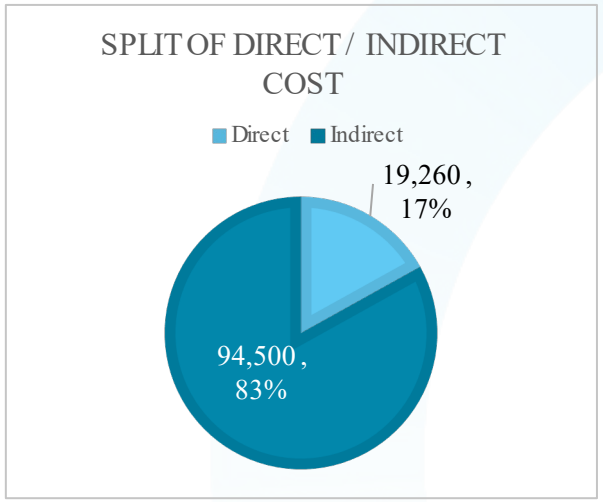
Reduced carbon emission

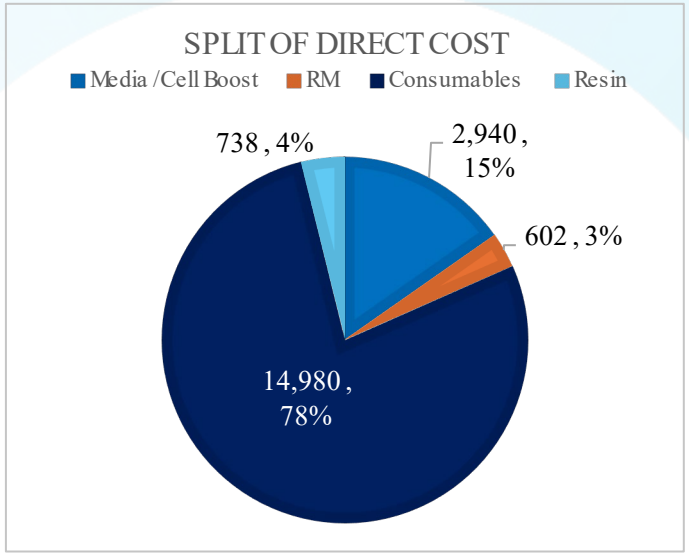
Up to 50% reduction in carbon emission

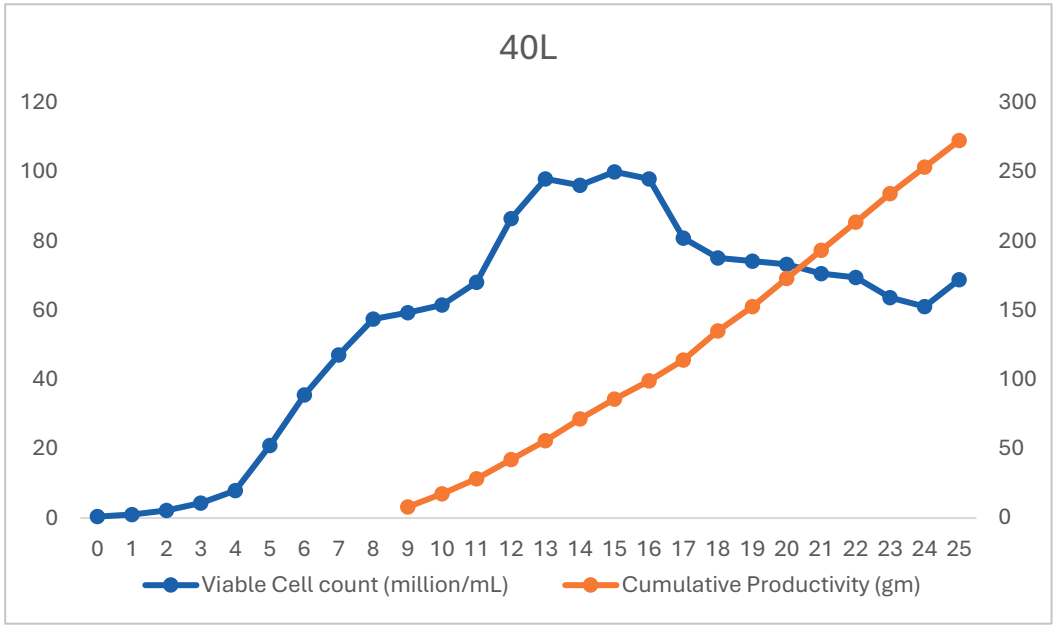
COGS for 50L D-mAb & 40L C-mAb

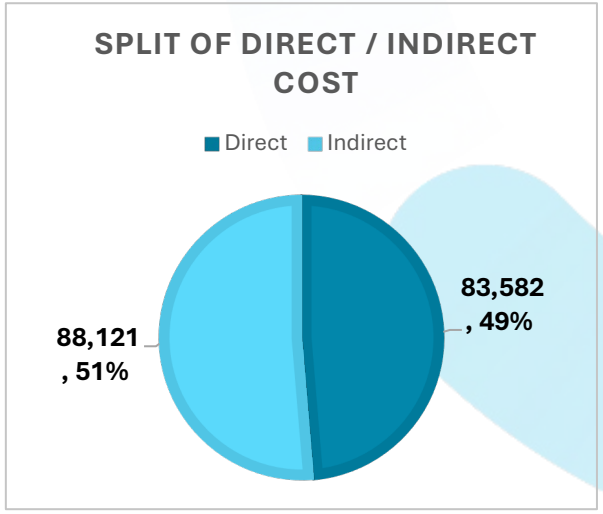
Scale	Output (grams)	Cost per gram (USD)
50L	32	3555
40L	178	965

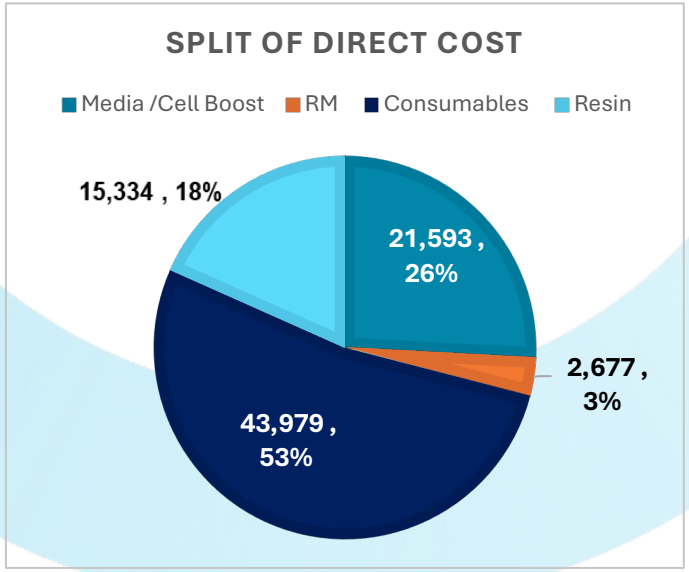






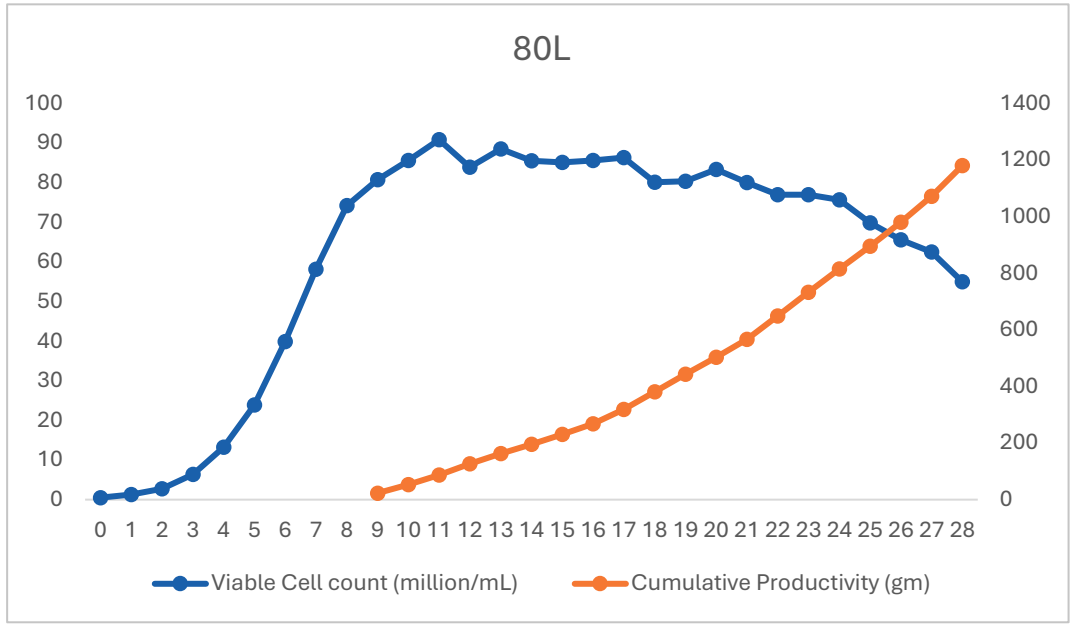


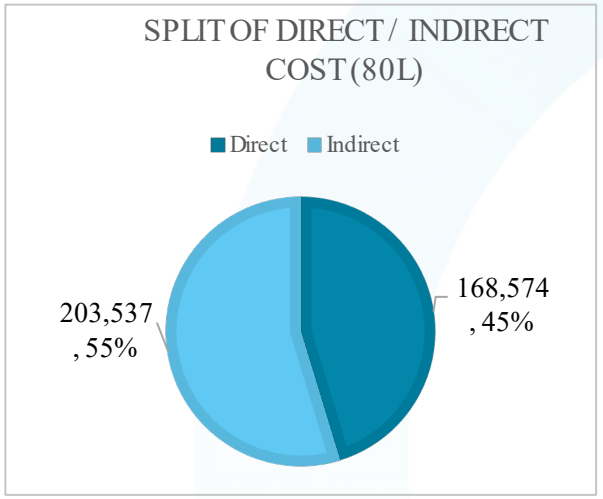


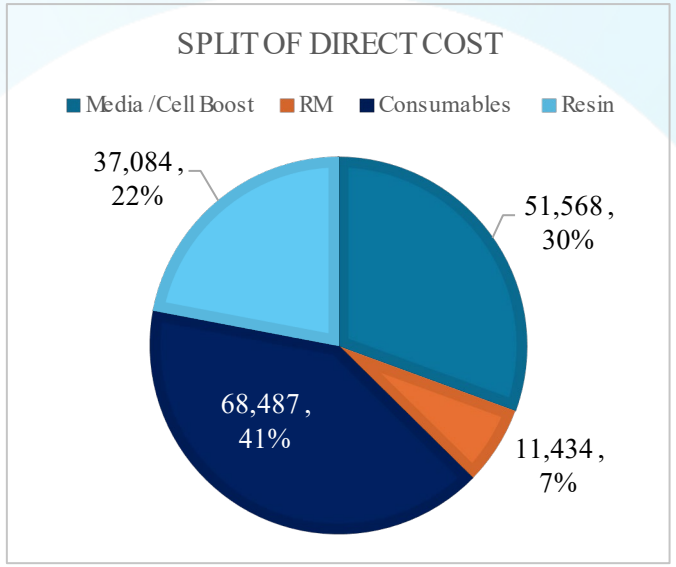


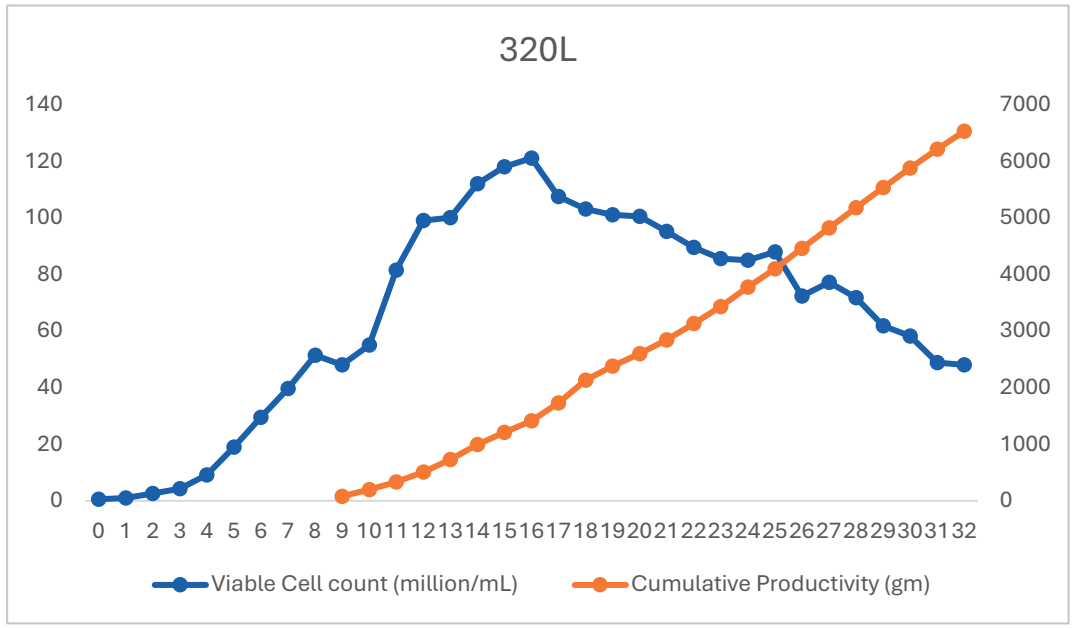
COGS for 80L & 320L perfusion for C-mAb

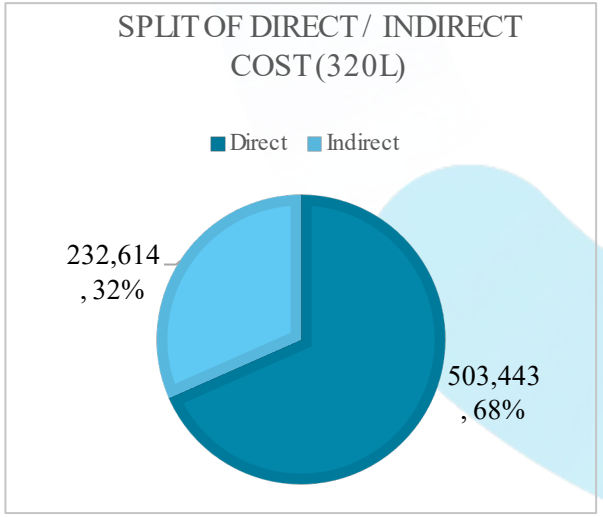
Scale	Output (grams)	Cost per gram (USD)
80L	698	533
320L	5008	147

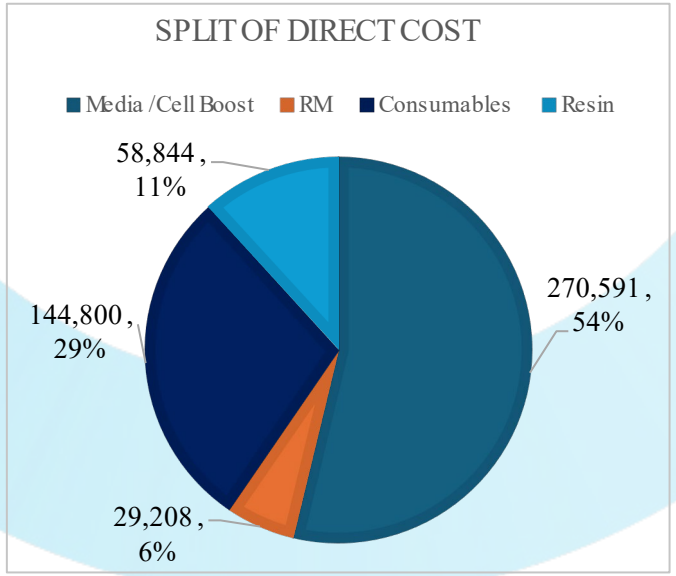




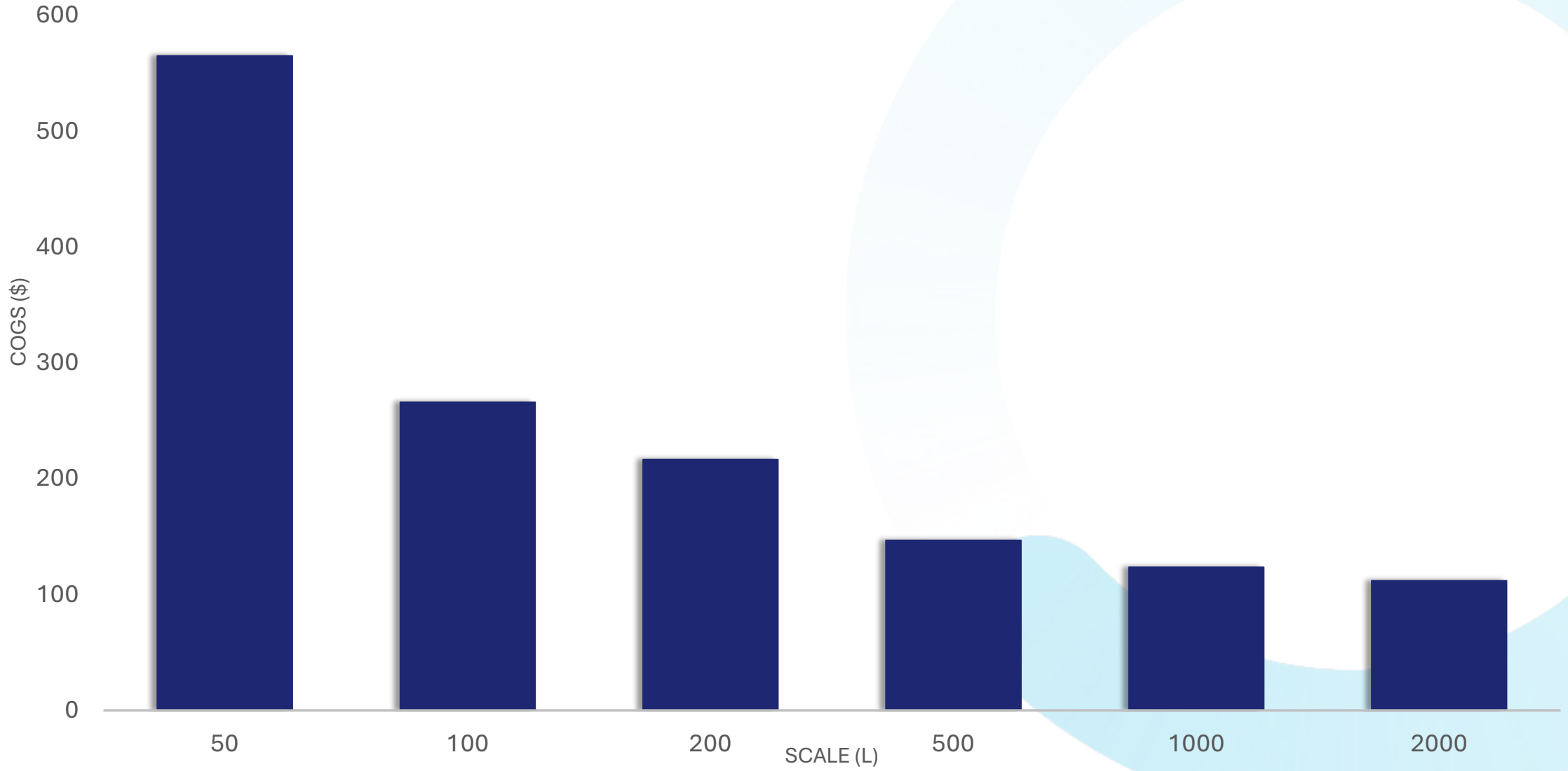






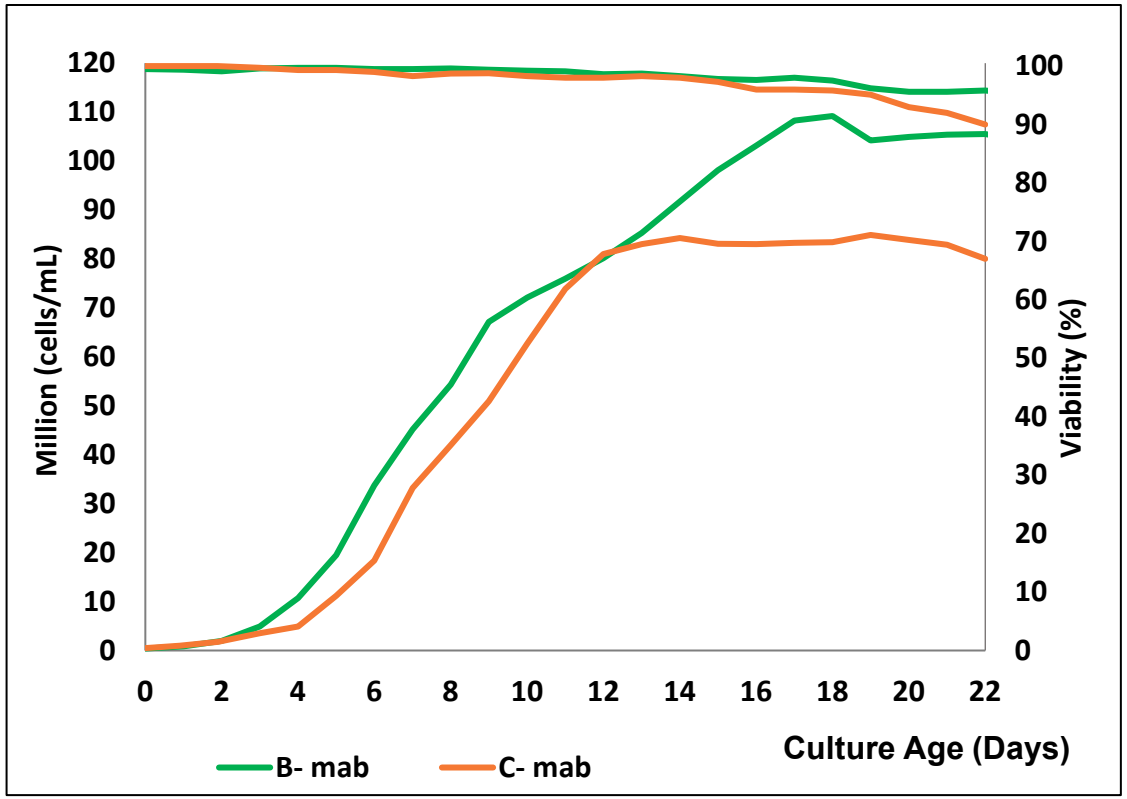


COGS Vs Scale for C-mAb

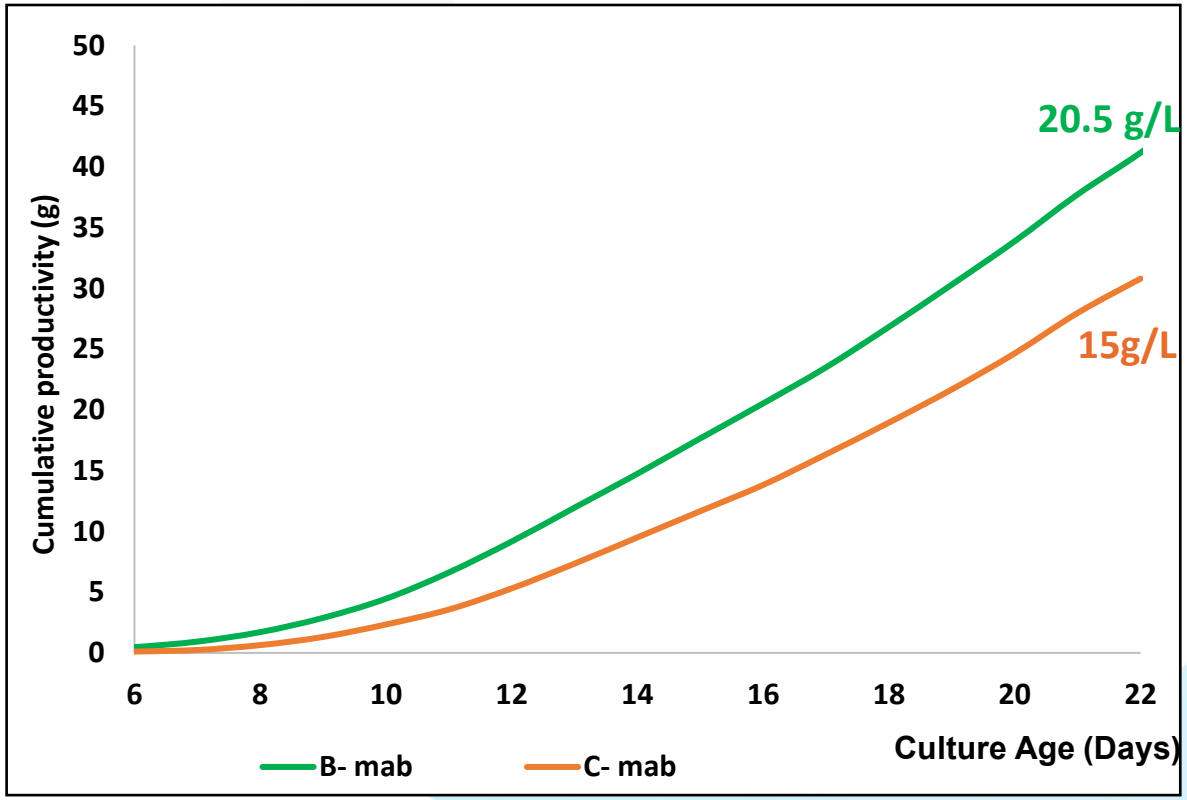


Productivity of C-mAb and B-mAb at 22 days

Growth Profile



Productivity



~1500
sq. ft.

~10-15
kgs/month

EnzeneX™ 2.0 is being upgraded to provide an even higher productivity, revolutionizing COGS per gram of protein manufactured

Blank Slate

http://dietplanreviews.info/goog/blank-slate.html
http://www.investinganswers.com/financial-dictionary/stock-valuation/cost-capital-112

Enzene Biosciences in the US

Q1 2025, we open our manufacturing facility in the US

Project type	Brownfield development
Location	New Jersey, East Coast
Size of facility	54,000 sq. ft.
Number of phases	Three
Phase 1 launch date	Q1 2025
GMP DS mfg. suite capability	500L Bioreactor (Phase 1) 500L Bioreactor (Phase 2) 2x 2000L Bioreactor (Phase 3)
GMP DP mfg. suite capability	One for formulation and small-volume filling equipment
Other facilities	QC lab, development lab, warehouse, freezer rooms, cell bank store

Continuous expansion:
Preparing for phase 2 development and beyond

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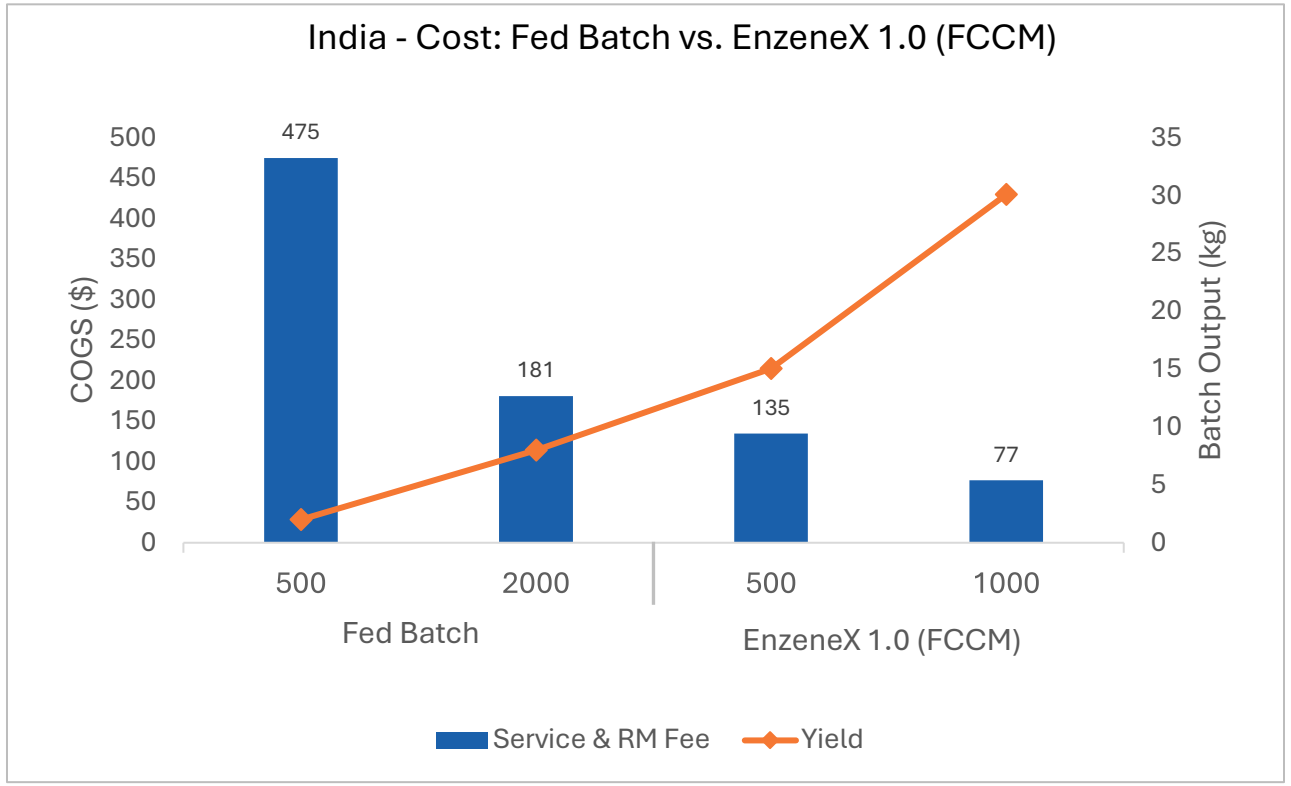
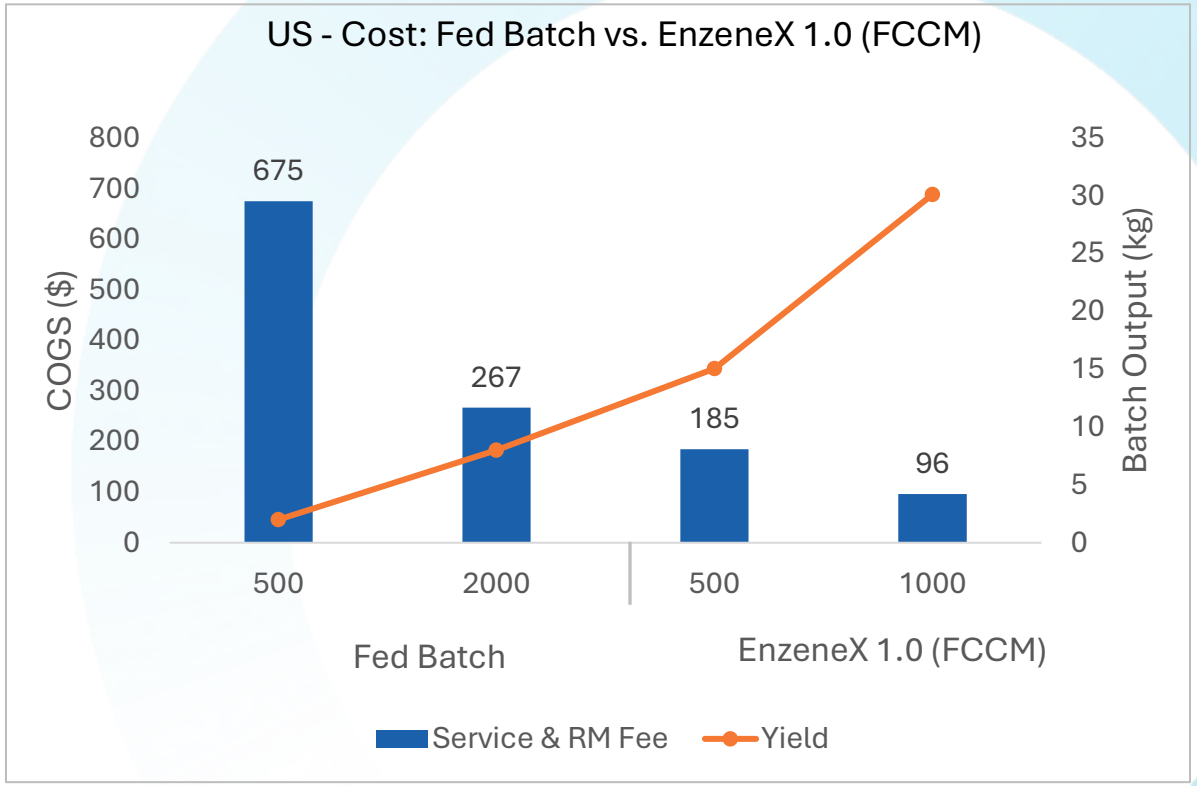
COGS per gram of protein: Fed-batch vs EnzeneX™1.0 (FCCM)





*Service Fees plus raw materials

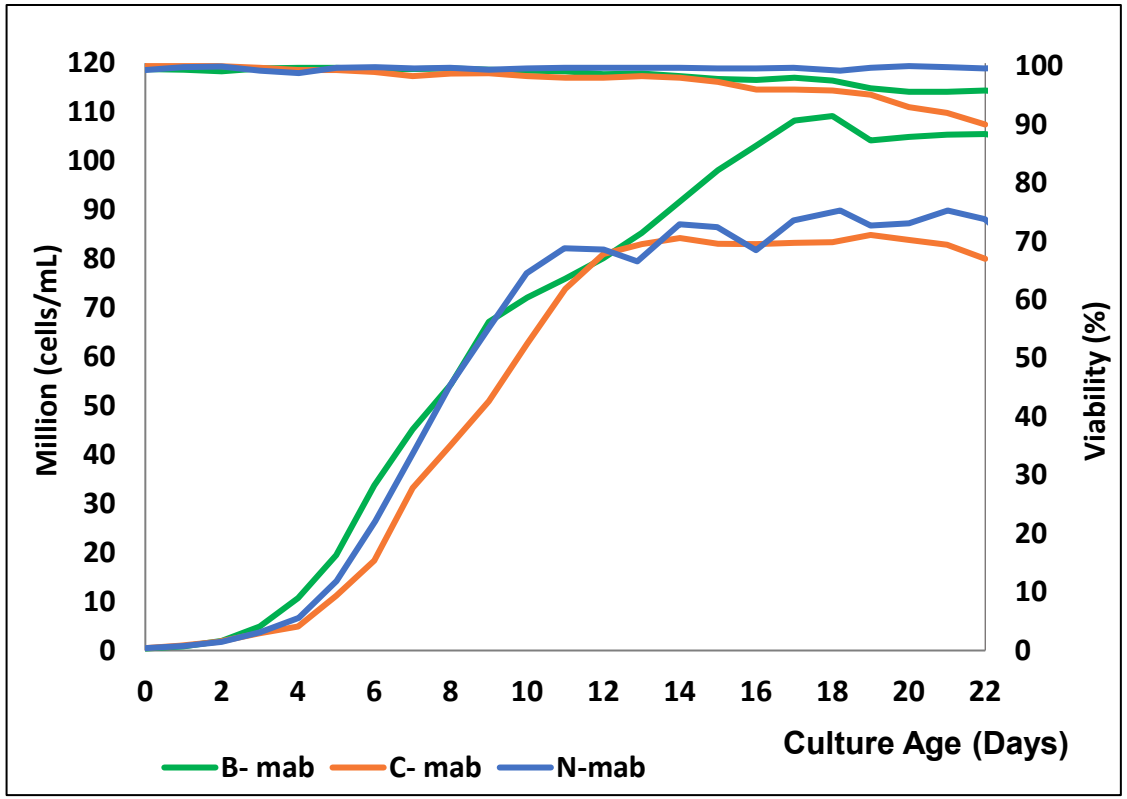
Ambitions for EnzeneX™ 2.0 (coming soon)

Reducing mAb production costs to $40 per gram

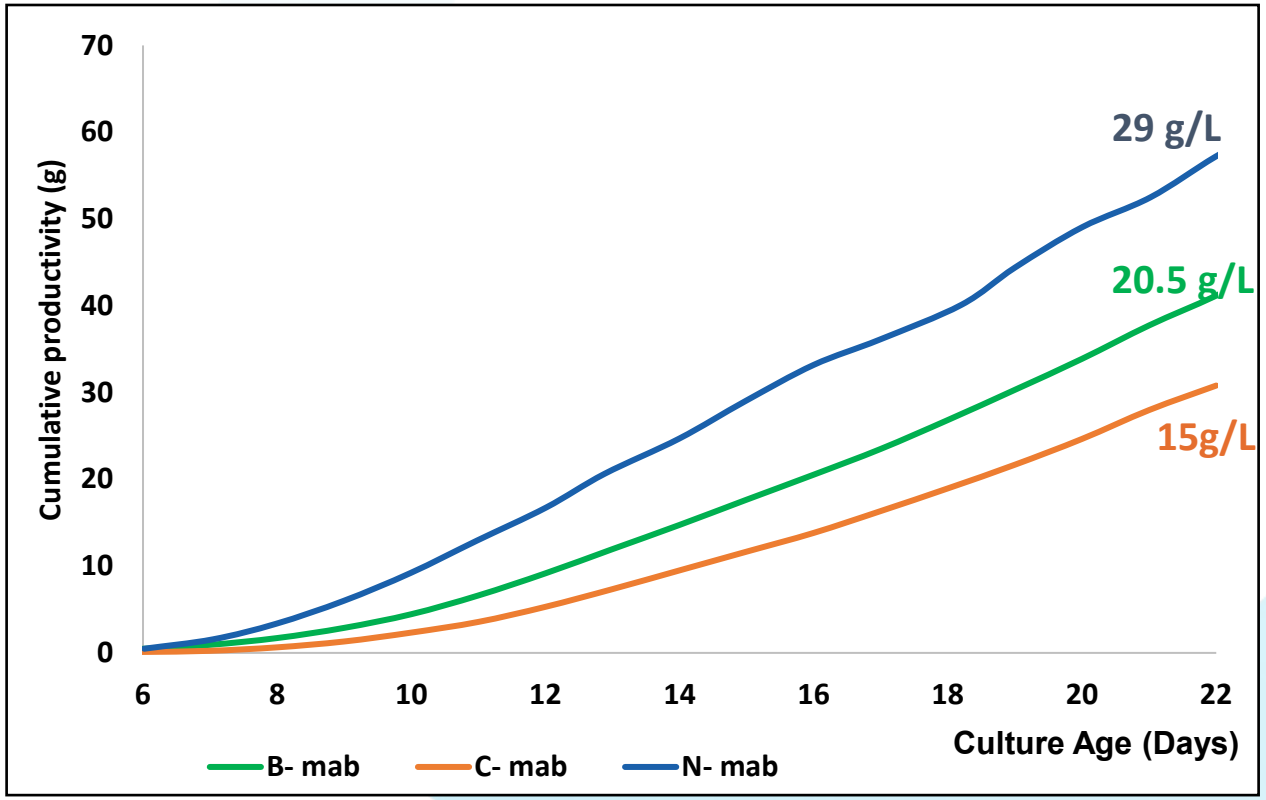
- Target yield of **40 kgs per month** from a 1000L FCCM batch
- Current productivity rate of **60g/L**

Enhanced productivity of N-mAb at 22 days with EnzeneX™ 2.0

Growth Profile



Productivity



The real opportunity is in bringing affordable medicines to patients

Source:
https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/alkem-subsidiary-enzene-launches-adalimumab-biosimilar-in-india/articleshow/98187974.cms

...Enzene launches adalimumab biosimilar in India

Synopsis: Enzene or its parent Alkem which is commercializing the drug didn't announce the price, but said it would be competitively priced.

Pune-based Enzene Biosciences, subsidiary of Alkem Laboratories on Thursday said it has begun commercial supplies of Adalimumab Biosimilar used for treating autoimmune disease like rheumatoid arthritis and ankylosis spondylitis.

arent Alkem which is commercialising the drug didn't announce the price, but said it

Healthworld.com
From The Economic Times

Pune: Enzene Biosciences launched Cetuximab as the first biosimilar to cancer. Sold under the brand name Erbitux, Cetuximab is a therapeutic chimeric monoclonal antibody that is used as a targeted therapy for metastatic colorectal cancer (mCRC) and cancer of the head and neck.

businessline.

Enzene rolls out biosimilar of Roche's cancer drug bevacizumab

Updated June 20, 2023 at 05:50 PM.

Through partnerships with drugmakers, Enzene Biosciences expects its biosimilar of bevacizumab to be cheaper than other generics

BY PT JYOTI DATTA

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Thank you

Passion. Innovation. Life.