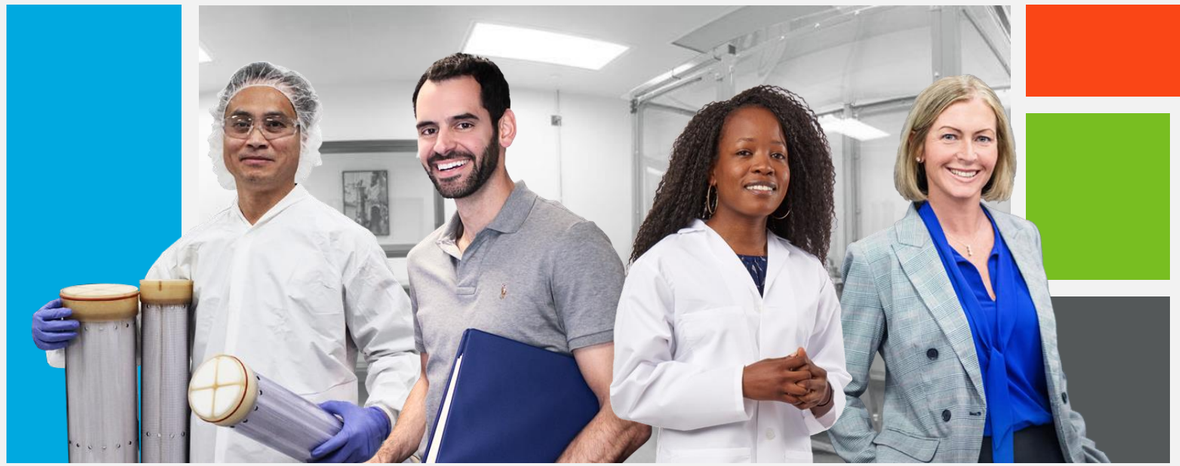
# Upstream intensification with XCell ATF® Technology
# More cells. More product. Faster.

Frederik Ottoy
District Sales Manager



August 21, 2022

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# Transforming bioprocessing through high impact technology innovation

## First to market with innovative solutions


| OPUS® R<br>Pre-packed Columns | XCell ATF®<br>Single-use Systems | KrosFlo® Integrated<br>Single-use Skids | TangenX® Single-use<br>Flat Sheet TFF Cassettes | Slope Spectroscopy®<br>Analytics |
|---|---|---|---|---|

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# Agenda

Benefits of XCell ATF® Intensification

XCell ATF® Technology

XCell ATF® Applications for specific challenges

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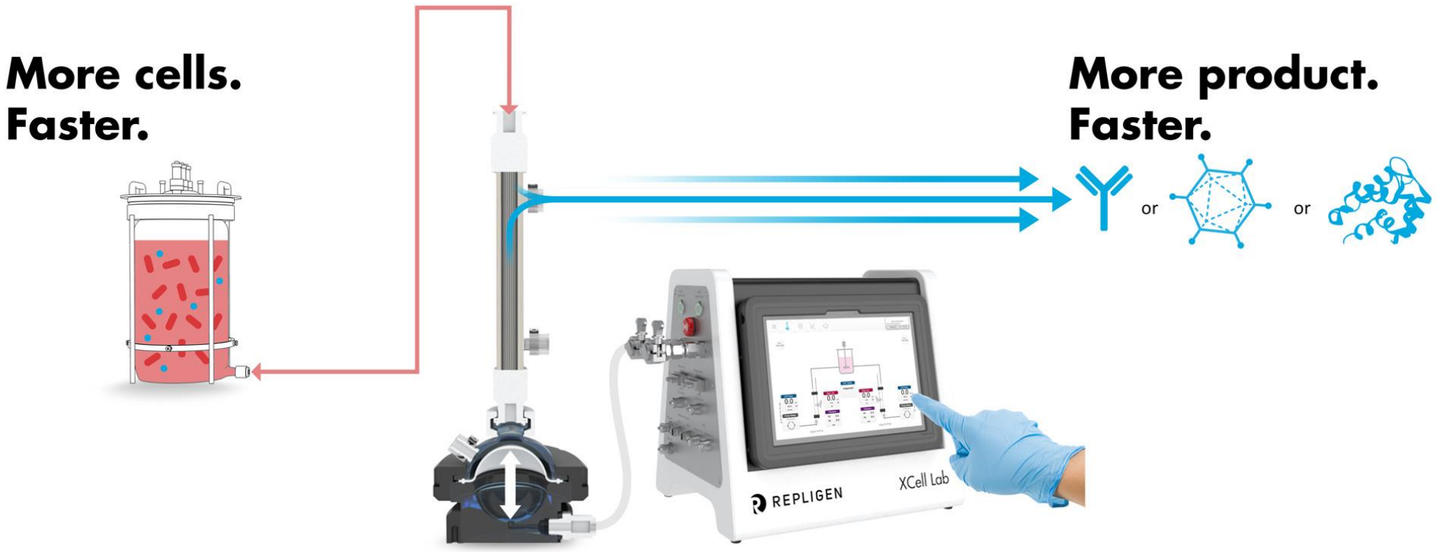
# XCell ATF® intensification solves manufacturing capacity, productivity, throughput challenges

## Fast and easy Fed-Batch and continuous intensification that scales to manufacturing




### DELIVER MORE, FASTER

**Increase throughput:**
more programs,
more molecules

**Increase productivity:**
more product per batch

**Increase capacity:**
more batches per facility

### EXECUTE HIGH ROI BUSINESS DECISIONS

**Reduce bioreactor size up to 10 fold**
for example from 10,000 L to 1,000 L

**Accelerate your program**
with smaller, flexible, intensified processes

**Re-think facility expansion**
lower cost, lower risk, faster results

### XCELL™ LAB CONTROLLER

NEW

**Design simplicity:**
software, hardware, device

**Precision pumping** enables robust development

**More process data** for improved characterization

**Reduced development media cost**

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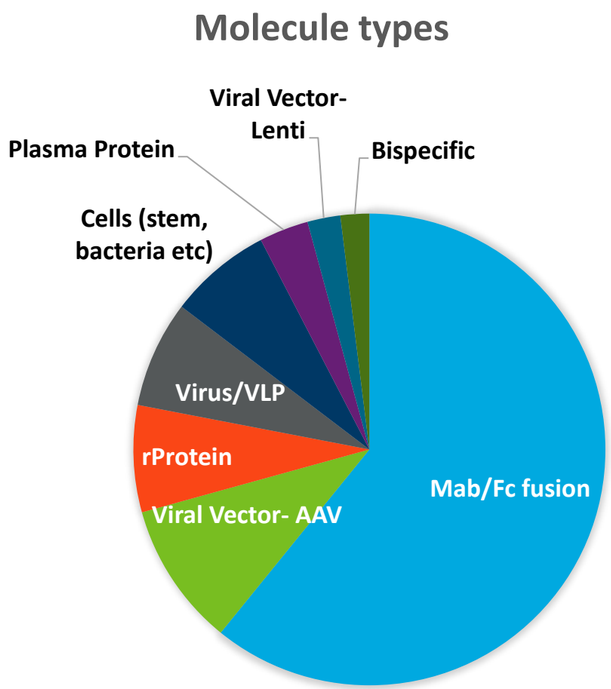
# Broad industry adoption across multiple platforms

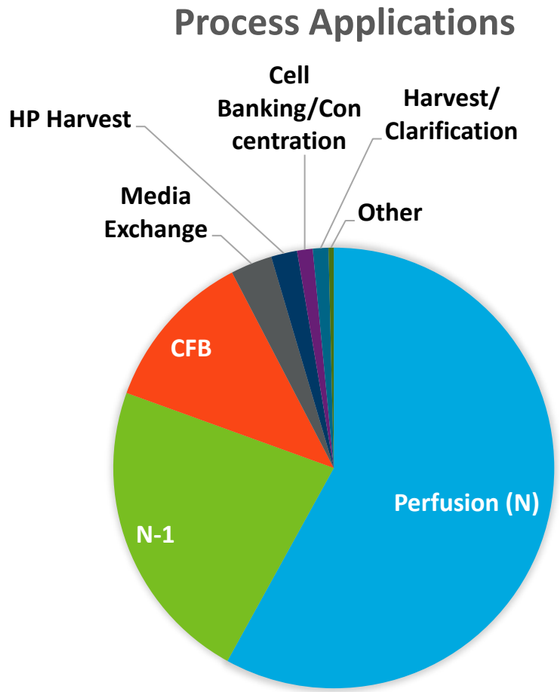
## Broad Platform Adoption

- Active at > **400** sites globally
- Large CMOs all over the world (North America, South America, Europe and Asia)

## Large Pipeline

- **>40** commercial processes in 9 countries
- **>30** processes currently in late phase/P3
- **Hundreds** in tox/preclinical, Ph1, Ph2

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# XCell ATF® installations across all sizes globally

## Transcenta intensified facility

"… with this technology and automated/connected intensified DSP, we can make >1 metric ton of DS in a facility with equipment that costs <$50M (greenfield) that can be built in 18 months from design… Not only that, but we can add capacity as needed and be ready in <12 months … **this is the future**."

Chris Hwang, CTO

## Sanofi integrated continuous facility near Boston

By Jim Haddadin
Daily News Staff
Follow
Posted Jan 24, 2018 at 9:08 PM
Updated Jan 24, 2018 at 9:08 PM

FRAMINGHAM — Sanofi Genzyme is doubling down on its investment in the Framingham Technology Park.

The drug maker plans to increase the size of its ongoing expansion project in Framingham with a two-story, 14,821-square-foot addition to its new building at the corner of New York and California avenues.

Representatives of the company are scheduled to appear before the Planning Board Thursday to discuss the project, which requires amendments to the site plans approved by the board in January 2014 and 2017.

"The construction at 2-8 New York Ave. in Framingham is to expand Sanofi's manufacturing production capacity in support of our portfolio and pipeline therapies," David Murdoch, Sanofi's director of communications for specialty care operations, wrote in an email Wednesday.

## WuXi Biologics bio 50% of capacity from 5-6% reactors

### WuXi Biologics: Zero to 220,000L of Capacity in 10 Years

by Dan Stanton
Wednesday, May 23, 2018 5:33 am

**WuXi Biologics has invested US$60 million to build a biomanufacturing facility in Singapore. By 2022, the CDMO will have 10 plants – an achievement it attributes to disposable and modular technologies.**

WuXi Biologics has announced plans to add a S$80 million (US$60 million) clinical and commercial biologics manufacturing in Singapore to its growing global network.

When operational, the site will boast 4,500 L biomanufacturing capacity comprised of two 2,000 L traditional fed-batch and one 500 L perfusion based continuous processing bioreactors.

## Samsung Biologics Korea adopts N-1 at 3,000L

### Samsung BioLogics Implements Large Scale N-1 Perfusion for Commercial Application

August 12, 2019

Incheon, S. Korea, Monday Aug. 12th, 2019 – Samsung BioLogics (SBL) has successfully performed N-1 (3,000L) perfusion with Alternating Tangential Flow (ATF) device to supply the 15,000L commercial production process in the Plant 3 facility at its manufacturing site in Songdo, S. Korea recently, reducing production time by up to 30% for the client.

With SBL's adoption of perfusion technology, clients may choose from a more diversified portfolio of manufacturing options. Perfusion is gaining broader biopharmaceutical application at small scale with clinical development, but few companies have reported utilization at large scale for commercial applications to intensify bioprocessing and boost productivity.

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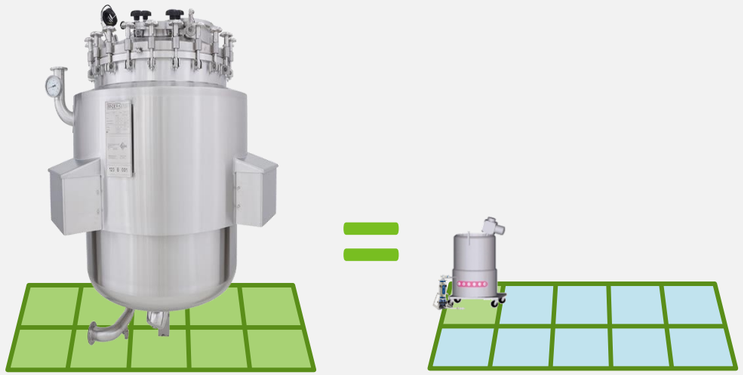
# XCell ATF® impacts facility level decisions

## More product in smaller facility in less time

- Solve facility fit-process challenges and **save millions**
- **Reduce bioreactor size**, but keep throughput
- **Achieve more** Fed-Batch runs per year per bioreactor
- Delay and **reduce significantly Capex** required to achieve more throughput

**“1/4 CAPEX, 1/3 OPEX, 1/10 footprint, 1/2 time”**

Kimball Hall, Ex VP Manufacturing, Amgen and Roche



**5,000L** = **500L + ATF**

**Smaller bioreactor creates more opportunities**

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# Intensify and simplify mAb and rProtein cell culture

## mAb and rProtein bioprocessing

### N-1 & N intensification with simplified clarification

- Eliminate centrifugation
- Eliminate depth filtration
- Fed-batch or continuous


### N-1 intensification with simplified clarification

- Eliminate centrifugation
- Reduce depth filtration
- Fast set-up


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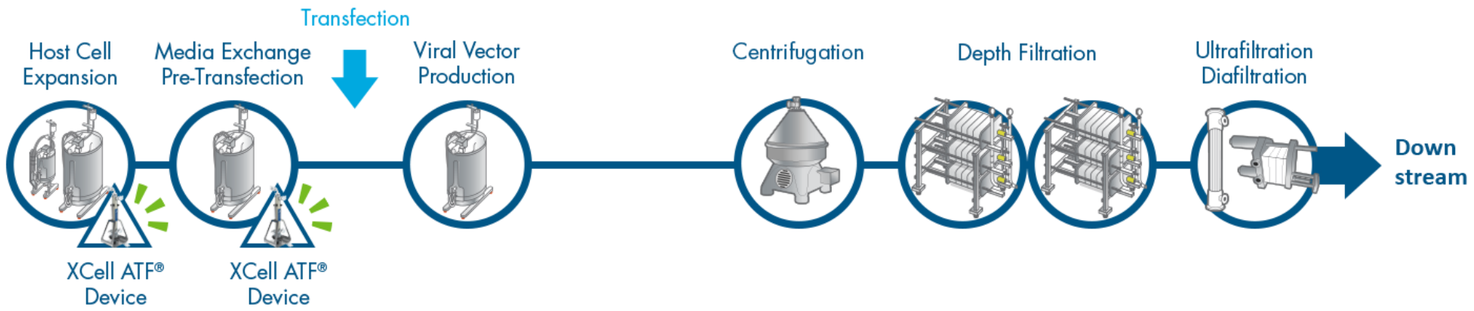
# Accelerate multiple upstream Gene Therapy and Vaccine unit operations

## Gene Therapy and Vaccine intensified manufacturing

### AAV production

- Boost output
- Save time




### Adenovirus and vaccine production

- Boost output
- Produce clarified harvest
- Go straight to downstream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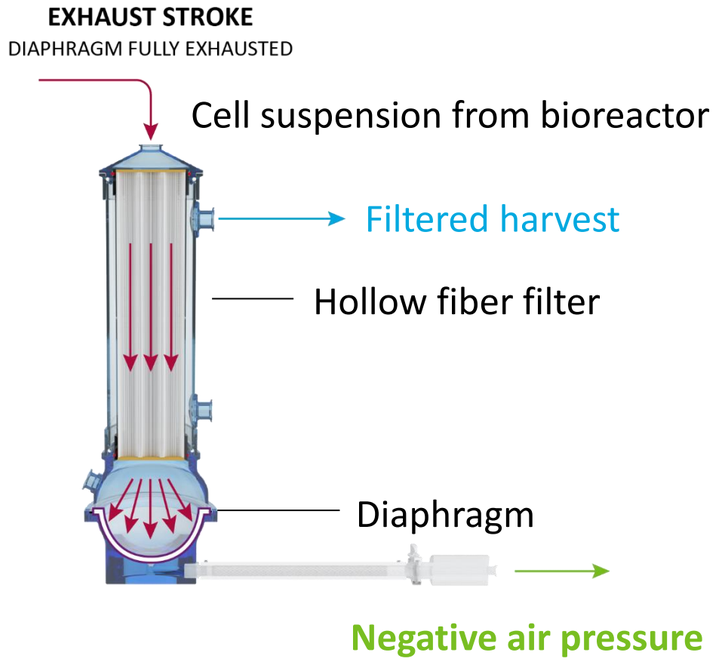
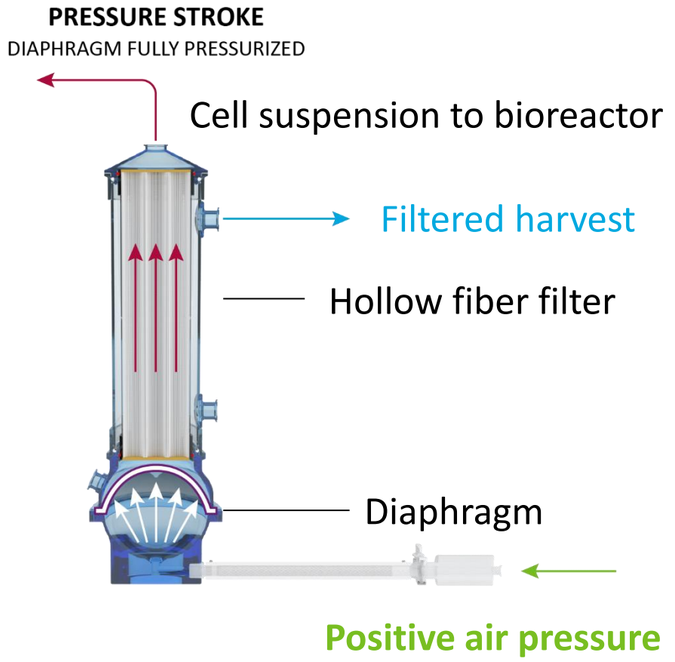
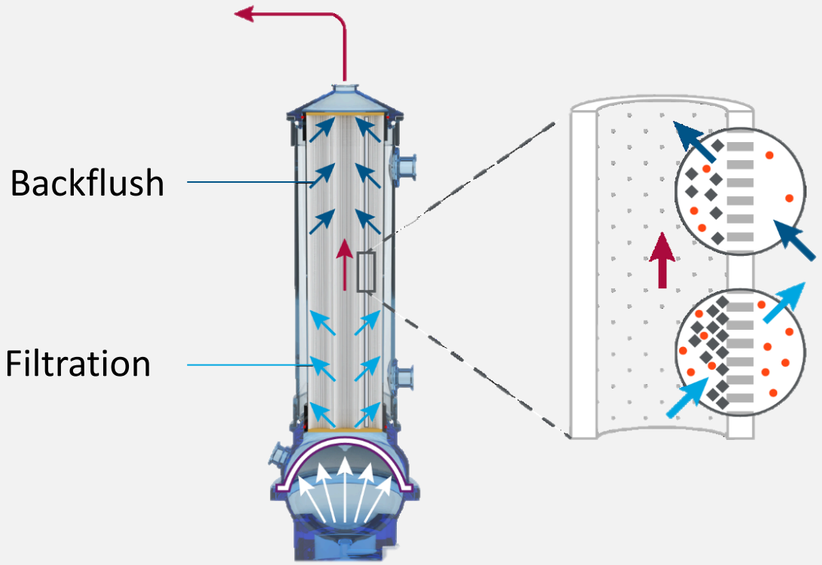
# Why *Alternating* Tangential Flow (ATF) works better

## Alternating flow cleans the filter allowing higher VCDs




Backflush *releases* components from wall

Filtration brings components to wall

- Product
- Cellular debris
- Membrane

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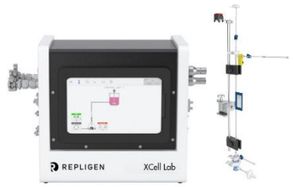
# Leverage XCell ATF® intensification from process development to manufacturing




Commercial rework

**Process development**
0.5 L – 50 L

Increased throughput and process data accelerate DOE.

**Clinical manufacturing**
50 L – 500 L

Increase throughput with many types of molecules. Mitigate facility expansion CAPEX and expenditure.

**MSAT**
0.5 L – 500 L

Full portfolio scale-up. Optimization with enhanced process controls.

**Commercial manufacturing**
500 – 5000 L

Increase bioreactor productivity with limited number of molecules. Reduce cost. Mitigate facility expansion CAPEX and expenditure.

New molecules

Go faster → Reduce costs

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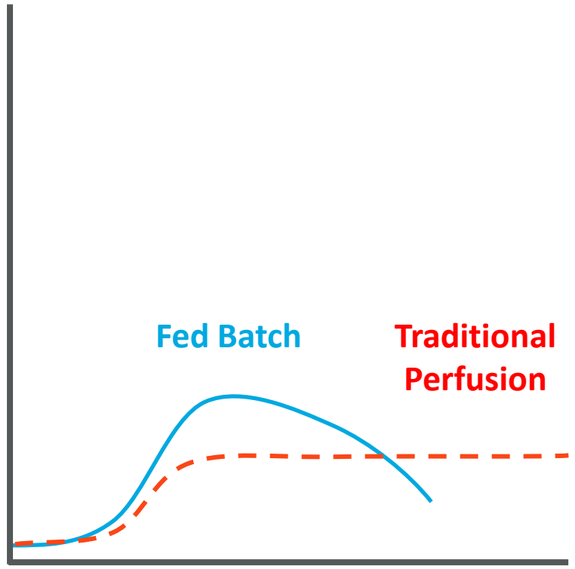
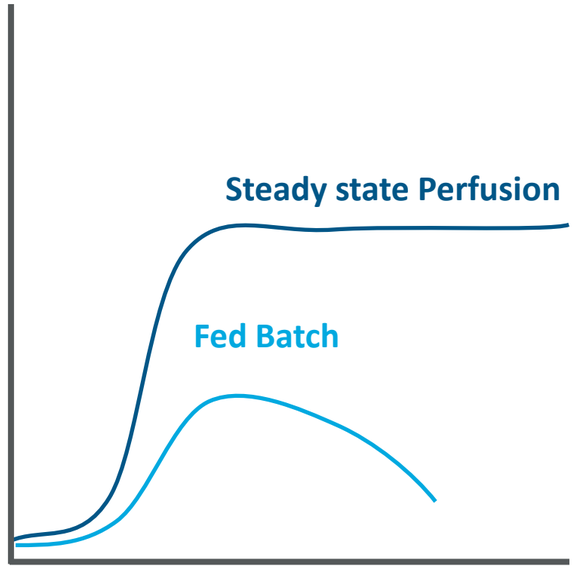
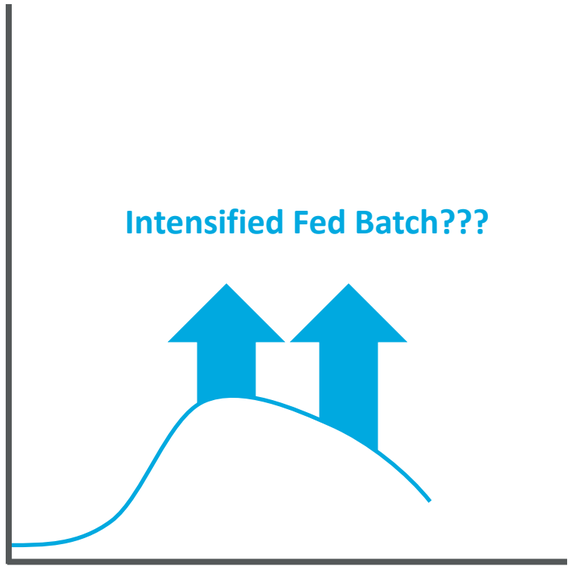
# XCell ATF® applications for specific challenges

# Cell retention applications now desired for Fed-Batch, not just perfusion




**Centrifuges and spin filter based perfusion**

**XCell ATF® based steady state perfusion**

What intensification options exist for Fed-Batch?

- How can you intensify **Fed-Batch -** *without implementing continuous*?
- How can you intensify **viral vector and vaccine processes?**

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# XCell ATF® applications

## Typical customer journey

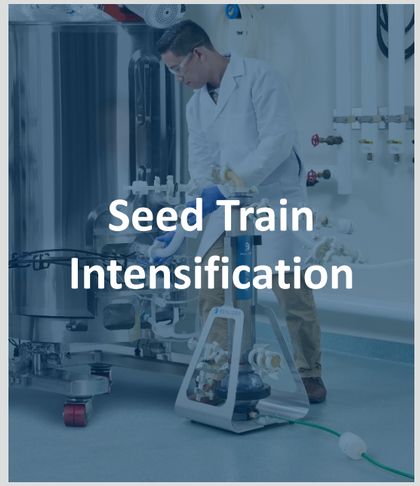

Pre- and Post-
Infection / Transfection
Intensification


N-1 Intensification

High Productivity
Harvest


Long-term perfusion
for mAbs and rProteins

N-1 with Perfusion




Accelerated
cell expansion

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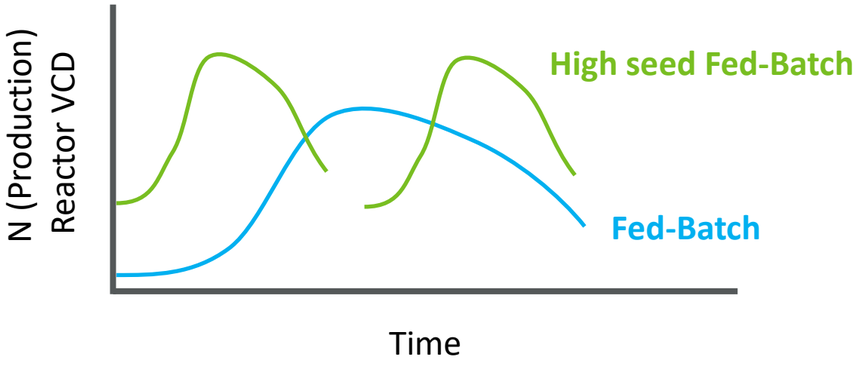
# XCell ATF® Fed-Batch applications increase throughput and/or yield

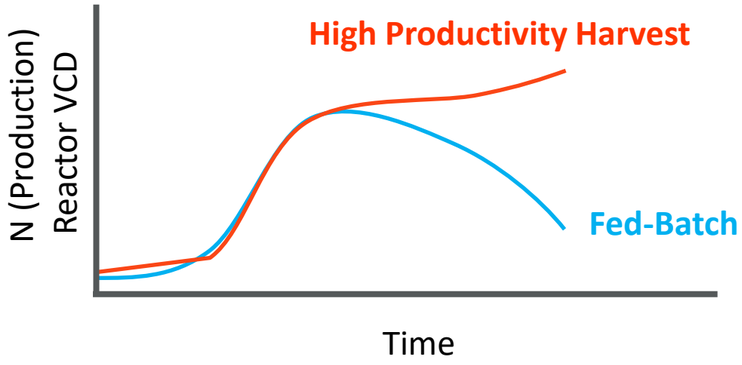
## N-1 Intensification

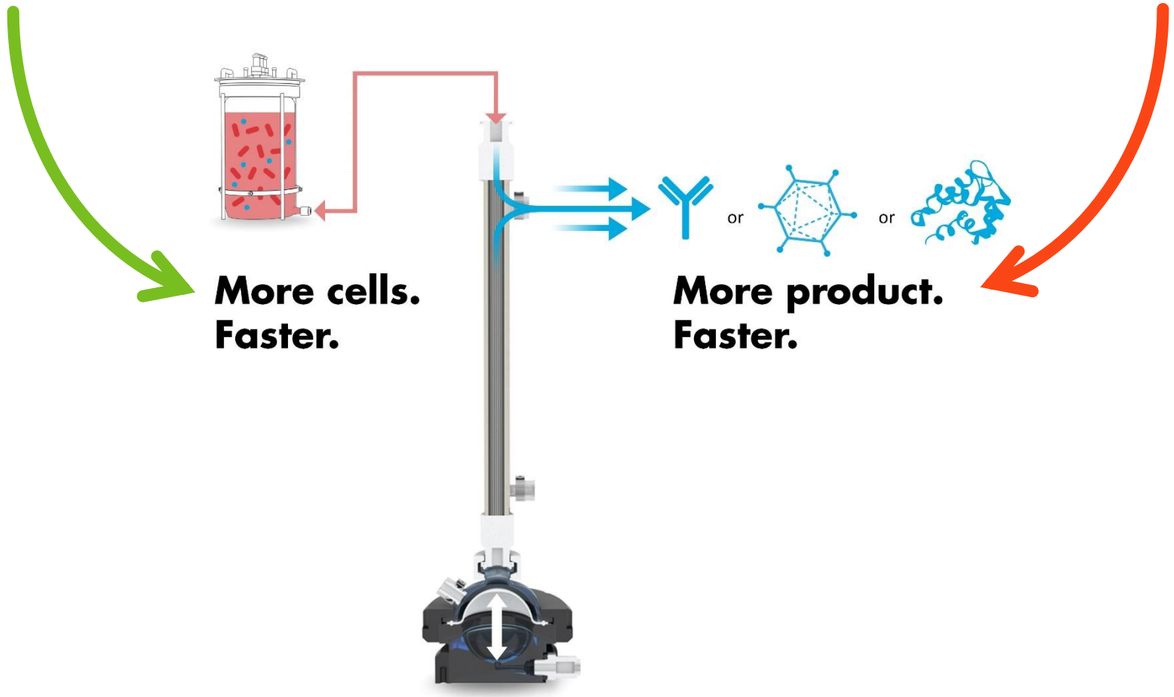
**Goal:** more batches of shorter duration, similar titer, single harvest with low regulatory impact




## High Productivity Harvest (HPH)

**Goal:** similar N batch duration, higher titer, single harvest with low regulatory impact

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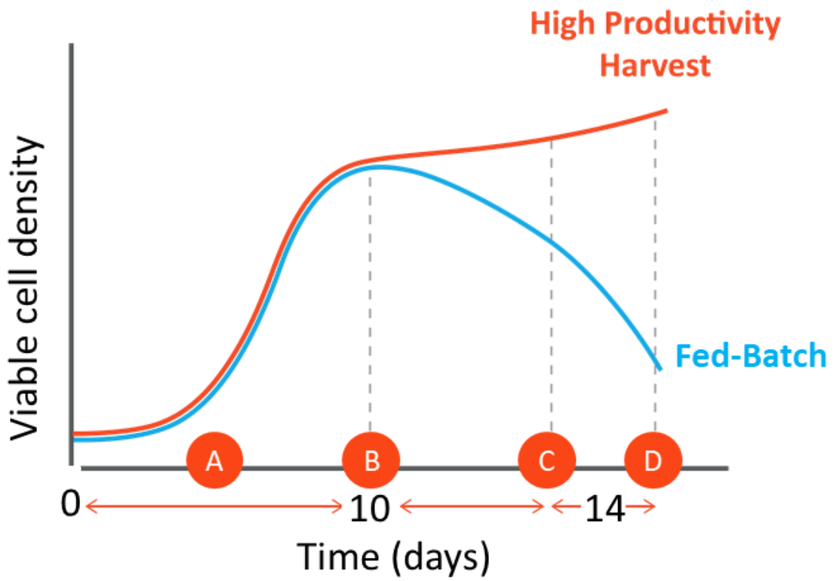
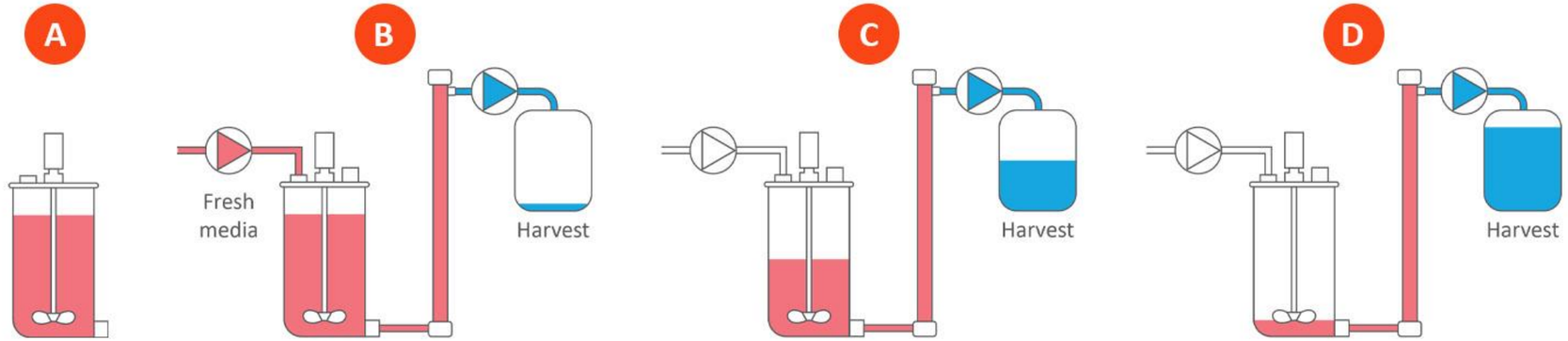
# High Productivity Harvest intensifies fed-batch




A) Start fed-batch process
B) Initiate harvest, replenish media
C) Draw down
D) Finish process




**Typical Fed-Batch process**

**Initiate harvest and replenish media**

**Start of bioreactor draw down**

**Finish HPH and Clarification**

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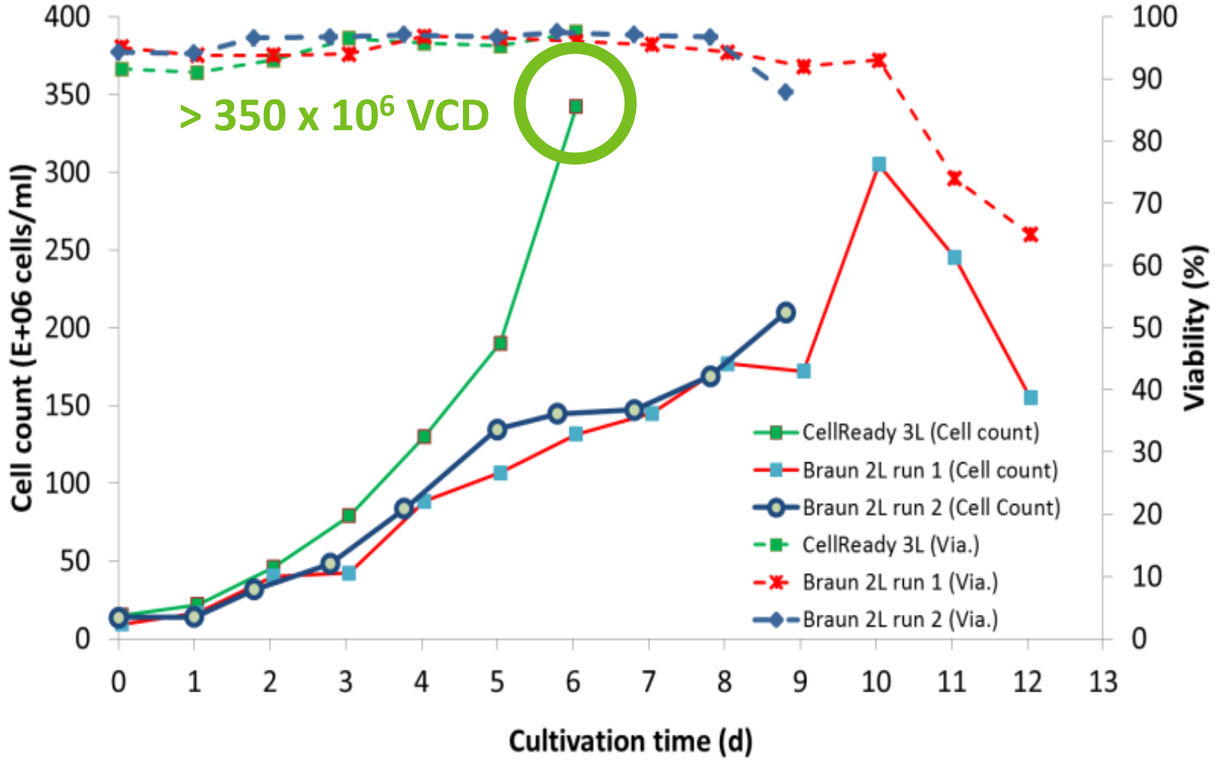
# Intensified insect line increases productivity and lowers COGS




- > 10X VCD compared to Fed-Batch (30 x $10^6$)
- 50% reduction in time
- 20-fold increase in productivity
- Lower COGs

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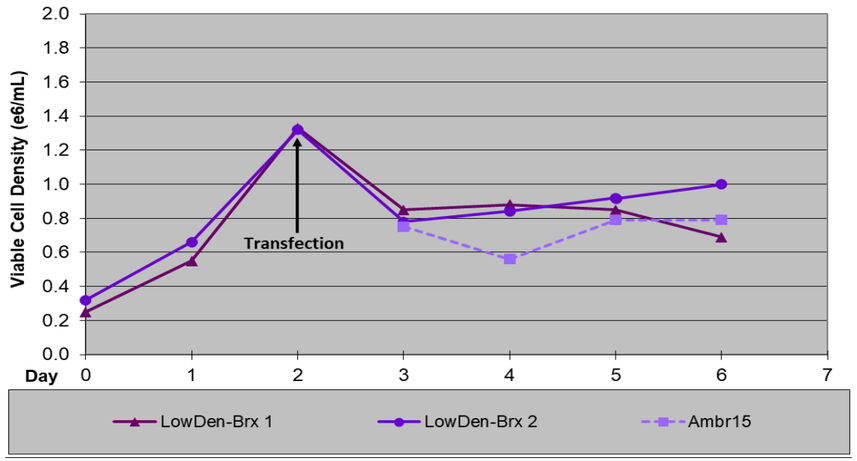
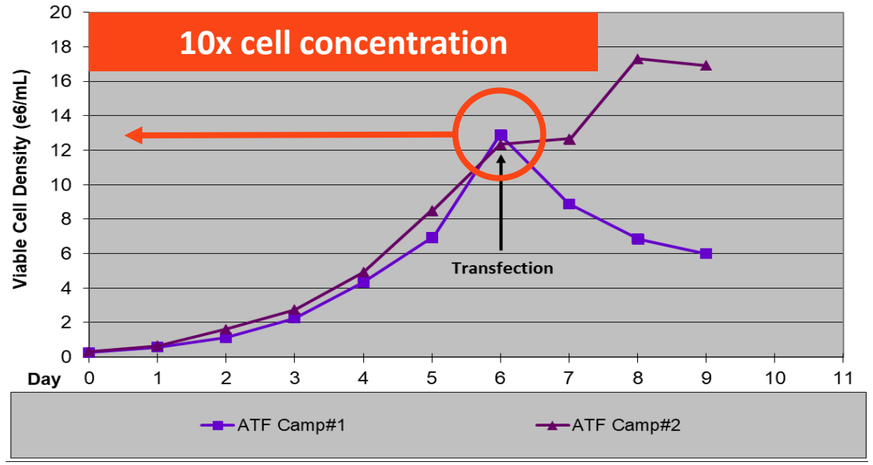
# Increased pre-transfection viable cell density and total capsid titer (N-1)

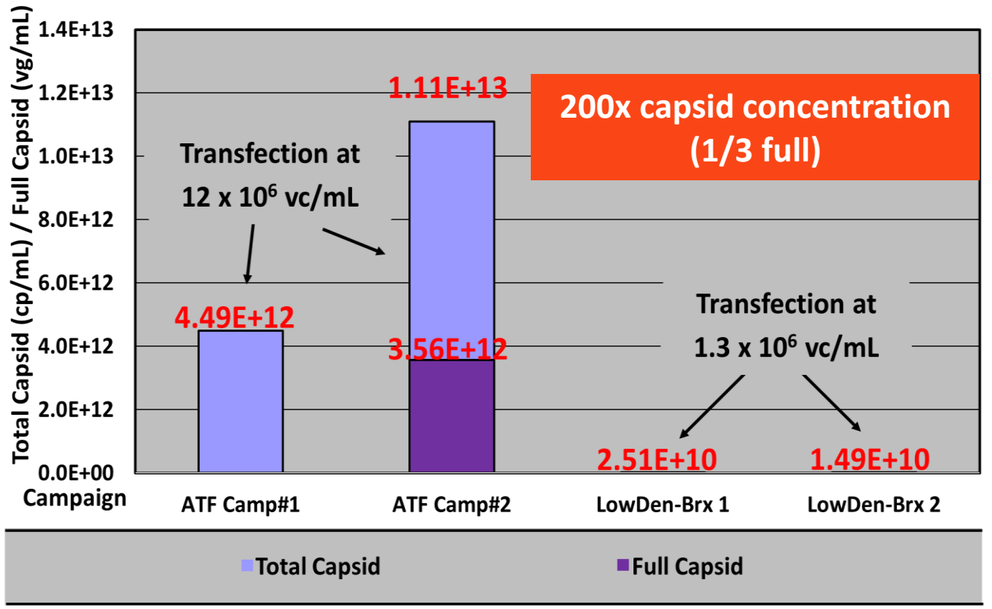
## Standard Fed-Batch AAV




## XCell ATF® intensified AAV




## Viral vector titer comparison




Source: Christa Short, High Cell Density Perfusion for the Production of AAV2 Viral Vector Using the Repligen XCell ATF® System. Repligen Technical Seminar, Burlingame, CA, Oct 17 2019

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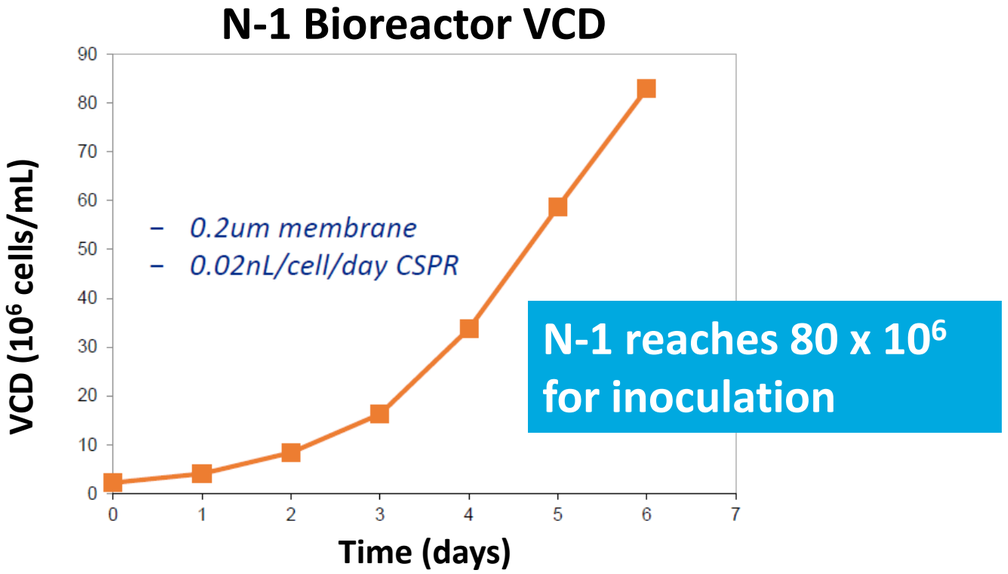
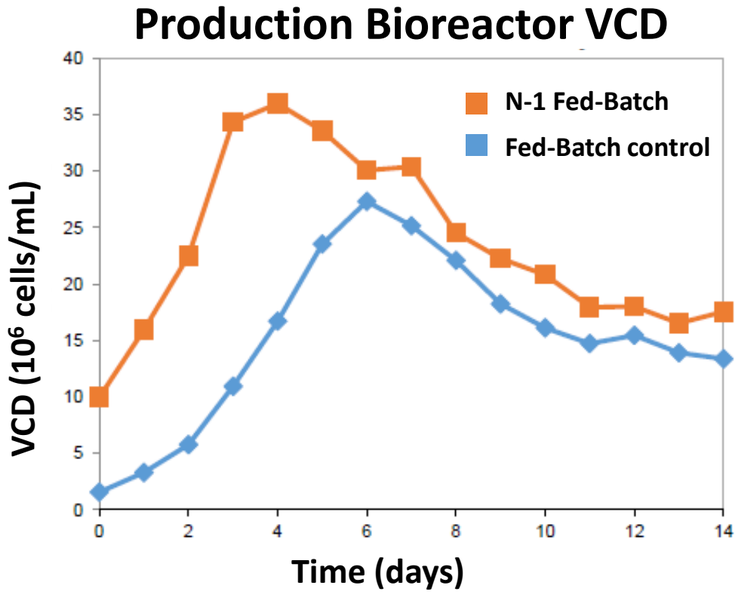
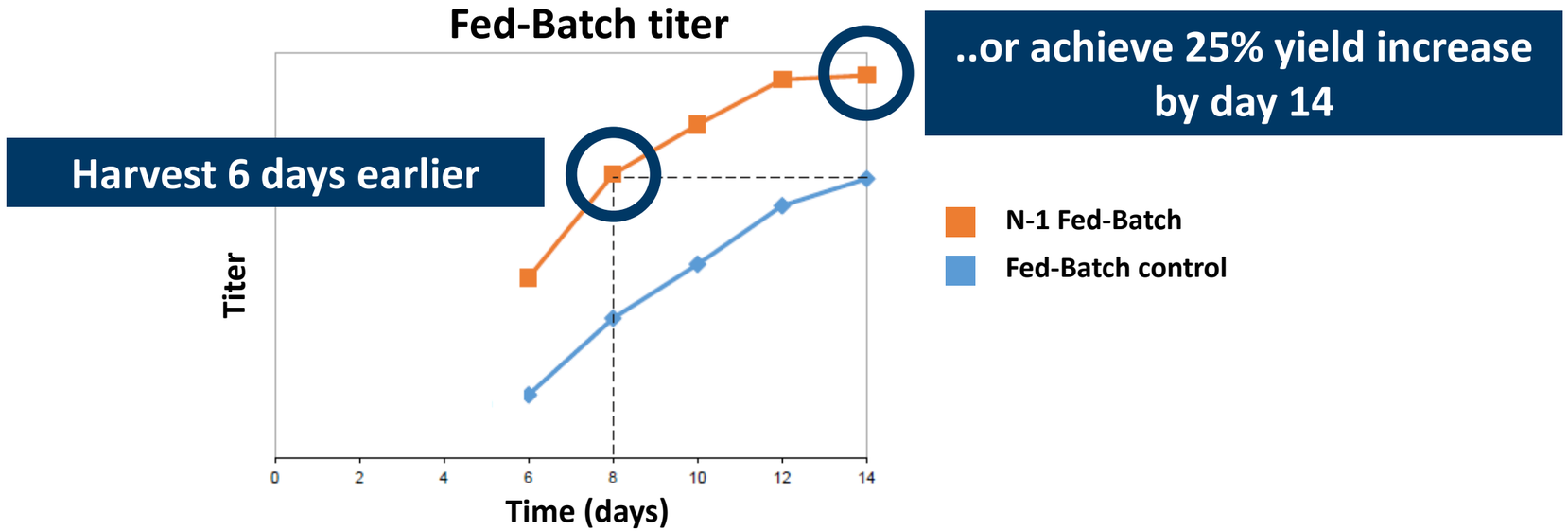
CYTOvance Biologics
a Hepalink Company

# N-1 fed-batch customer success

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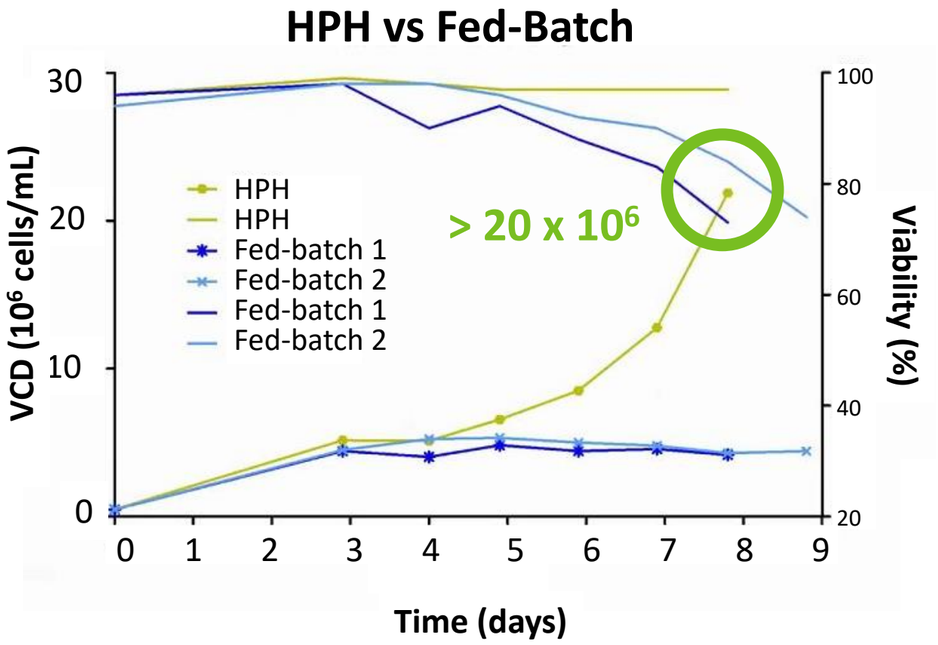
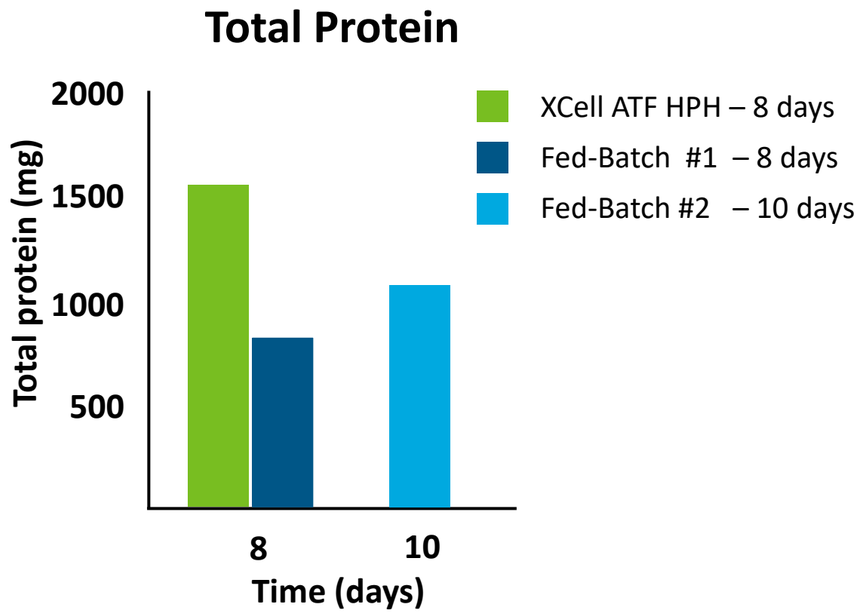
# High Productivity Harvest (HPH) customer success




- VCD increased ~4X
- Viability maintained near 100%




- 2X total protein
- Same, or fewer days, as Fed-Batch

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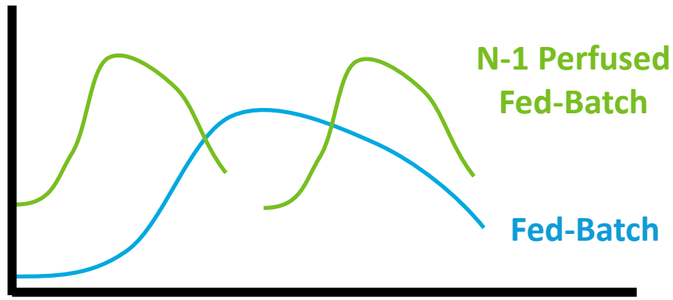
# XCell ATF® Fed-Batch applications address specific challenges

| | Process development<br>0.5L – 50 L | Clinical manufacturing<br>50L – 500L | MSAT<br>1L – 500L | Commercial manufacturing<br>500L+ |
|---|---|---|---|---|
| **N-1 boosts throughput** | + | + + + | + | + + + |
| | | More molecules | | More batches |
| **HPH boosts productivity** | + | + + | + | + + |
| | More product per run | | | |

## N-1 Perfusion

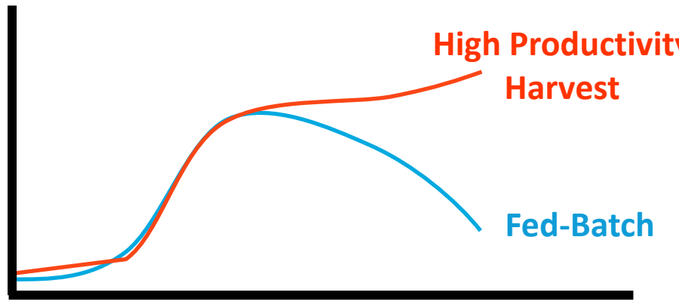
- High seed N reactor, similar titer
- Quicker reactor turnaround
- Throughput boost




N (Production) Reactor VCD and Time

## HPH

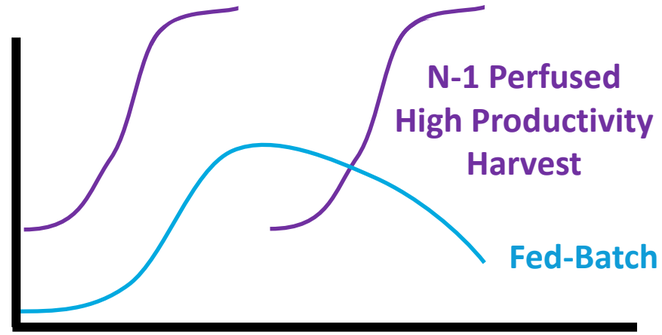
- Multi-harvest at high titer
- Eliminate centrifuge & DF
- Productivity boost




N (Production) Reactor VCD and Time

## Combined N-1 & HPH

- Quick reactor turnaround
- Productivity boost
- Eliminate centrifuge & DF




N (Production) Reactor VCD and Time

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# N-1 and HPH benefits over traditional Fed-Batch

Which option is best for you, for your facilities?

| | Fed-Batch | N-1 | HPH | N-1 and HPH |
|---|---|---|---|---|
| N reactor run time (days) | 14 | 7 | 14 | 7 |
| Single defined batch? | Yes | Yes | Yes | Yes |
| Media used at N stage (vessel volumes) | 1 | 1 | 1.5 – 4 | 1.5 – 4 |
| Harvest volume | 1 | 1 | 1.5 – 4 | 1.5 – 4 |
| Yield (normalized) | 100% | 100% | 100% - 200% | 100% - 200% |
| Output (normalized per unit time) | 1 | 2 | 1.2 – 2 | 2.4 – 4 |
| Centrifuge/DF required? | Yes | Yes | No | No |
| Ease of FB retrofit | n/a | ++ | + | + |
| Late phase adoption ease | n/a | ++ | + | + |

N-1 vs HPH selection balances time, yield, media and implementation

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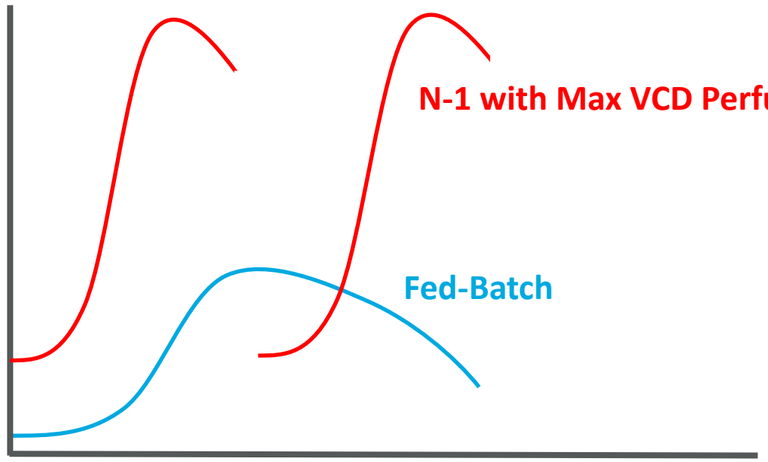
# Short and long duration perfusion options for maximizing output

Long-term perfusion for mAbs and rProteins

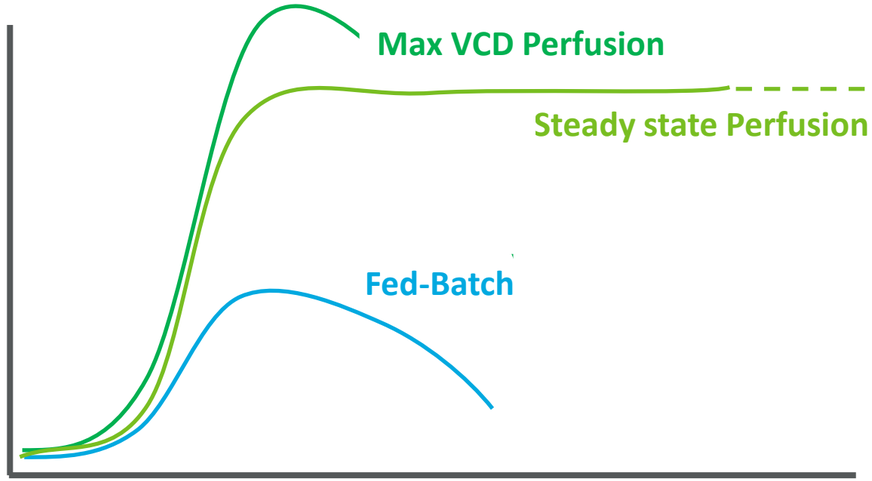
N-1 with Perfusion

N (Production) reactor VCD and time

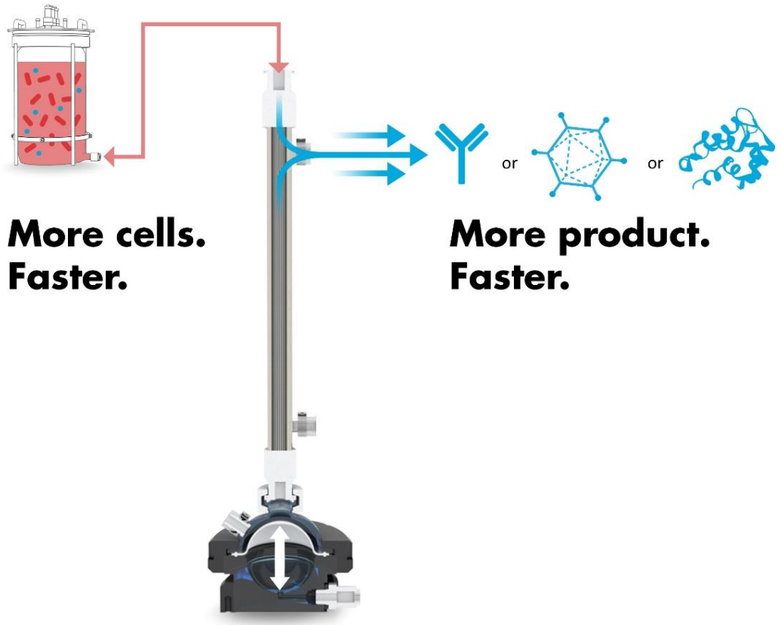



**More Cells AND More Product**

N (Production) reactor VCD and time




**More Product**

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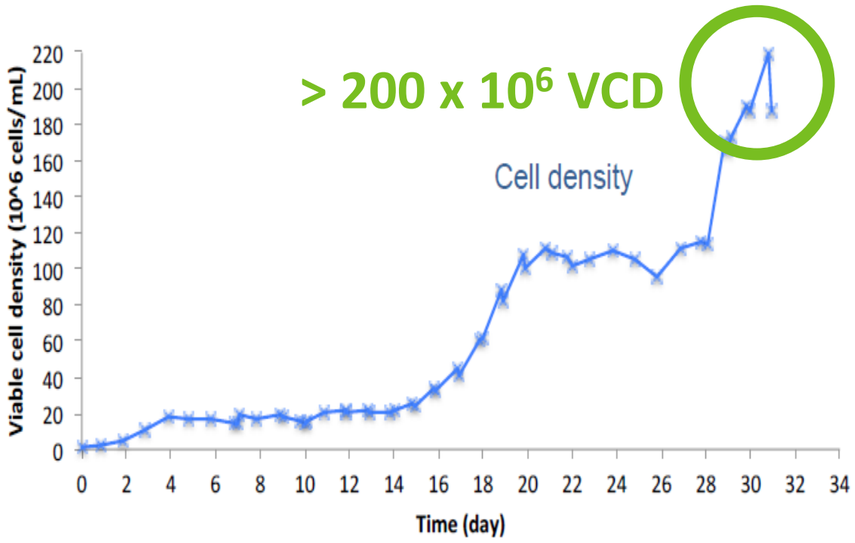
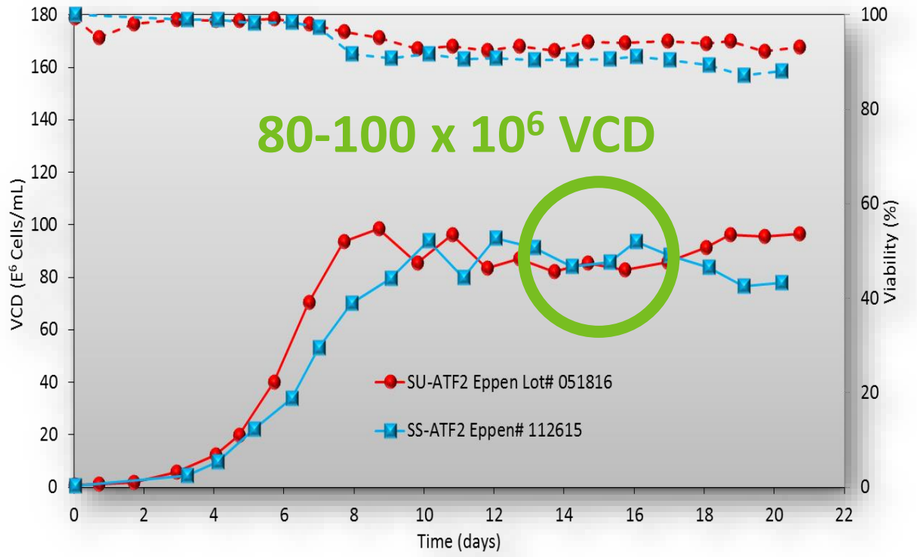
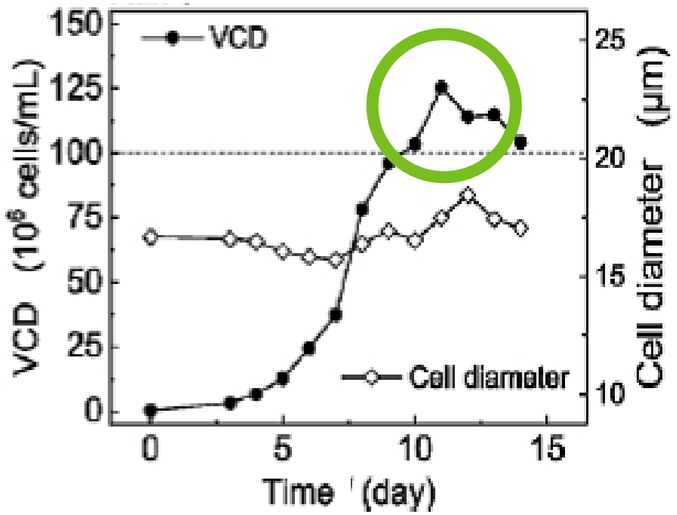
# Perfusion process reaches 10X VCD over Fed-Batch




- CHO, recombinant protein process
- Achieved 200 x $10^6$ VCD in university lab




- CHO, recombinant protein process
- Achieved 100 x $10^6$ VCD in industrial lab (<6 months)




> 125 x $10^6$ VCD

- CHO, recombinant protein process
- Achieved 110 x $10^6$ VCD in a pharmaceutical company

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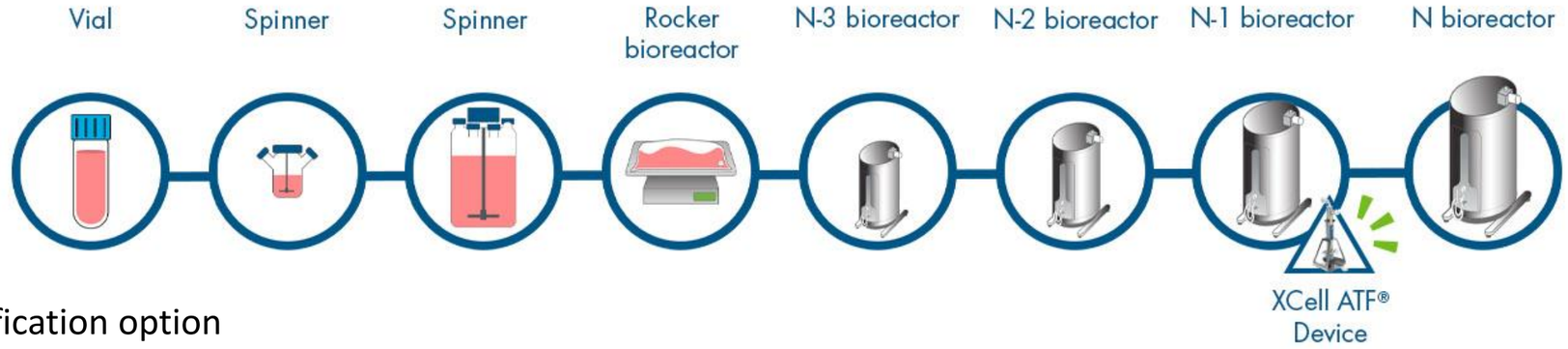
# Reduce steps and accelerate time to (N) production reactor through faster cell growth

XCell ATF® Device

## N-1 intensification

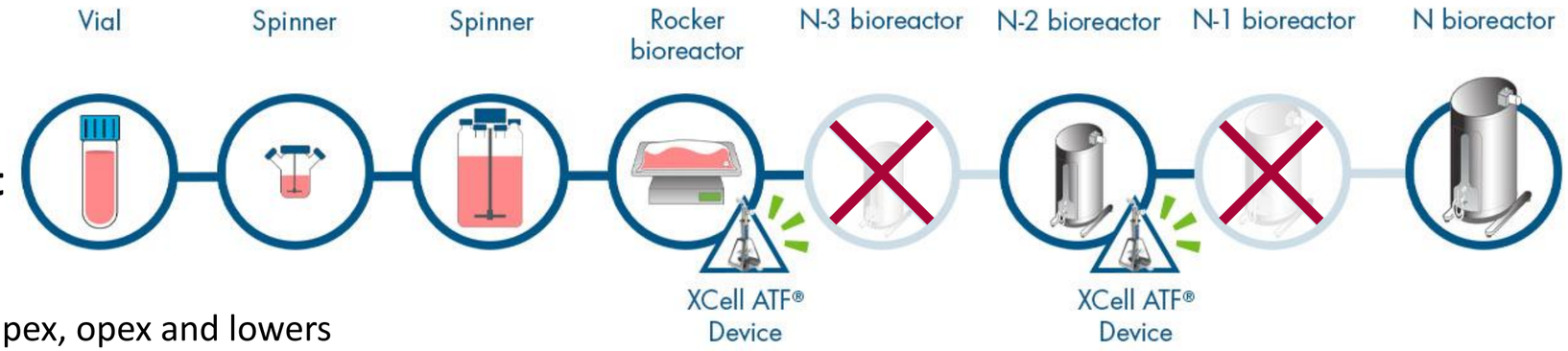
**8 Steps**
**~37 Days to product**




- Simplest seed intensification option
- Quicker bioreactor turn-around

## N-2 or earlier intensification

**6 Steps**
**~31 Days to product**




- Saves time, space, capex, opex and lowers validation risk due to fewer steps required

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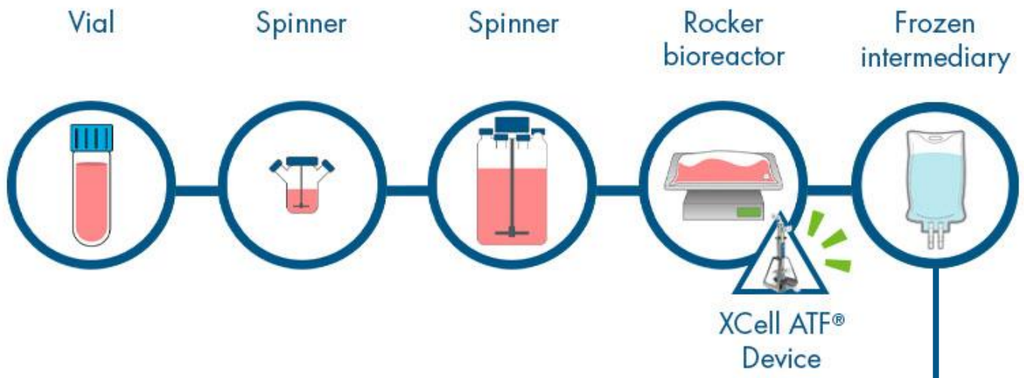
# Facilitate smaller and faster manufacturing platforms using frozen process intermediaries

## Large Volume High Density (LVHD) Frozen Process Intermediaries

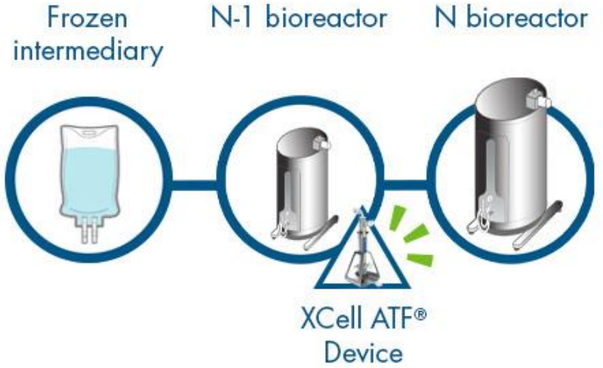
**Steps, time and location not relevant as outside production timeline**

- De-couple cell bank and variable early cell culture expansion from manufacturing




## Frozen Process Intermediaries with N-1 Intensification

**3 Steps**
**4 - 7 Days to production**




- R&D scale becomes commercial scale; reduce tech transfer
- Reduce capital requirements: cleanrooms, bioreactors and
- Maintain flexibility for final process selection: FB, Dynamic perfusion, CFB or long-term perfusion

XCell ATF® Device

REPLIGEN

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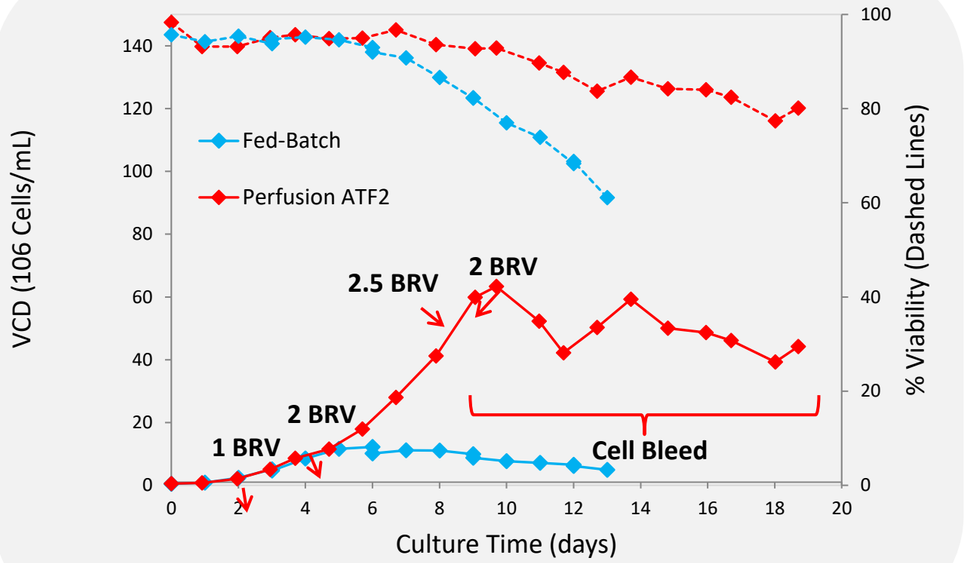
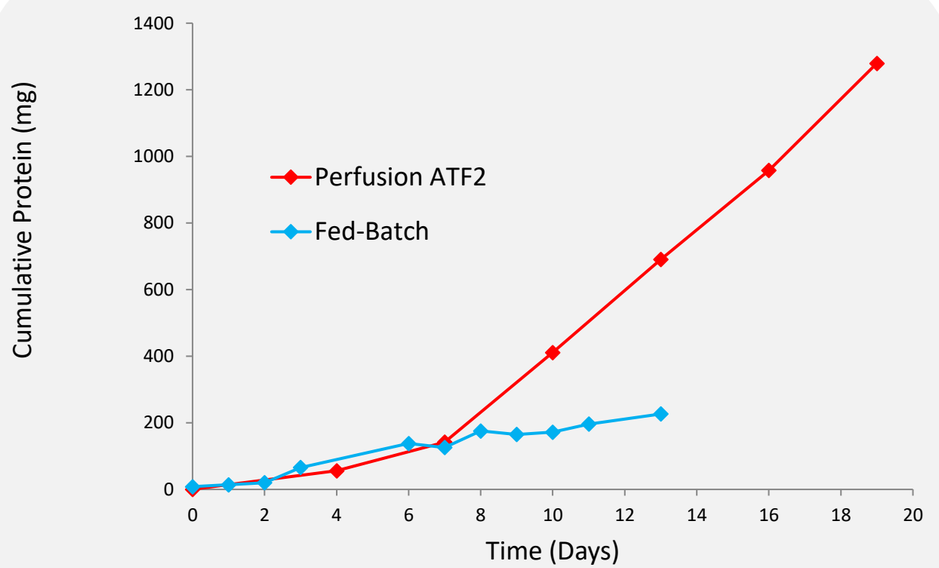
# Case Study: 1st run, swapping from FB to Perfusion

mAb production in CHO




- By Day 10 the cell density in XCell ATF® intensified BR is ~ $60e^6$ cells/mL vs $12e^6$ cells/mL in Fed-Batch
- Viability drops much quicker in Fed-Batch culture than XCell ATF® perfusion culture
- After 13 days, protein production is over 3 times higher in perfusion than Fed-Batch
- The total cumulative protein in XCell ATF® perfusion is ~6 times higher than fed-batch culture

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