Strategies for improving productivity and process economy with rocking bioreactors

Olof Larsson

Imagination at work

Biotechnology companies are consistently facing multiple types of challenges when it comes to delivering biologics. These challenges can be:

- Maximizing equipment utilization
- Improving process economy
- Reducing process times
- Simplifying operations

By meeting these challenges, biopharmaceutical companies can unlock their full potential in driving efficiency in biomanufacturing.

Agenda

Introduction

- New capabilities of rocking bioreactors in biopharmaceutical manufacturing

Rocking bioreactors in process development

- Scale-up/scale-down studies for high titer fed-batch cultures
- Adherent cell cultures with microcarriers

Strategies to intensify the seed train operations by means of perfusion

- The use of perfusion in a seed bioreactor culture, enabling a one-step process from high-density cell bank vial to production bioreactor
- The impact of an intensified seed train strategy on process economy

Novel strategies with ReadyToProcess WAVE™ 25 system

For years, the WAVE Bioreactor™ has been a platform of choice for seed train applications.

In this presentation, we hope to provide novel insights around using the WAVE 25 Bioreactor to drive efficiency in your seed train and process development applications.

New capabilities enable more advanced applications for rocking bioreactors

- Easier set-up and operations
- Improved physiochemical controls (pH, DO)
- Well-characterized engineering parameters for easier scale-up
- Improved perfusion functionality
- Improved rocking controls for low-shear processes
- Automation with UNICORN™ software

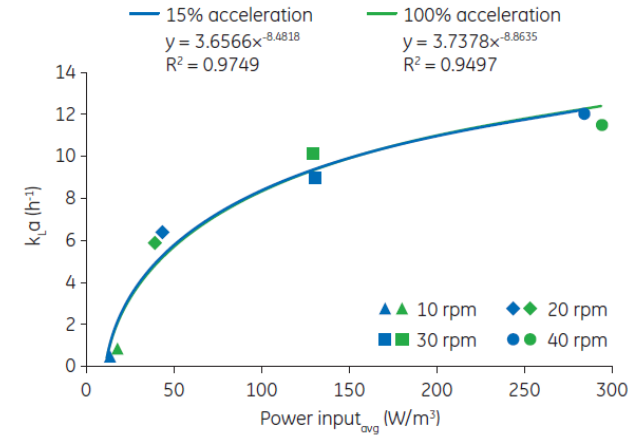
DO = dissolved oxygen

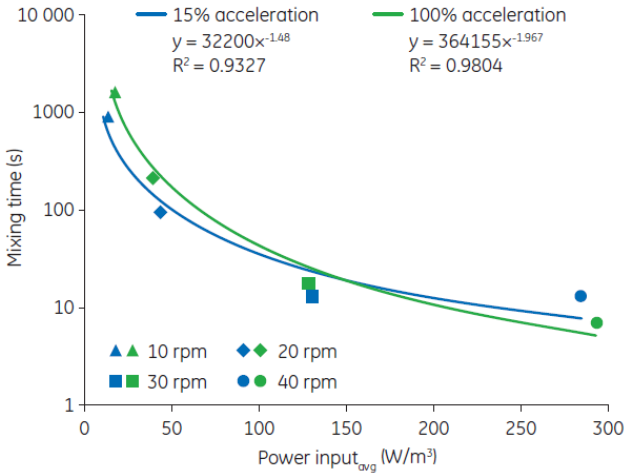
ReadyToProcess WAVE™ 25 as a tool in process development

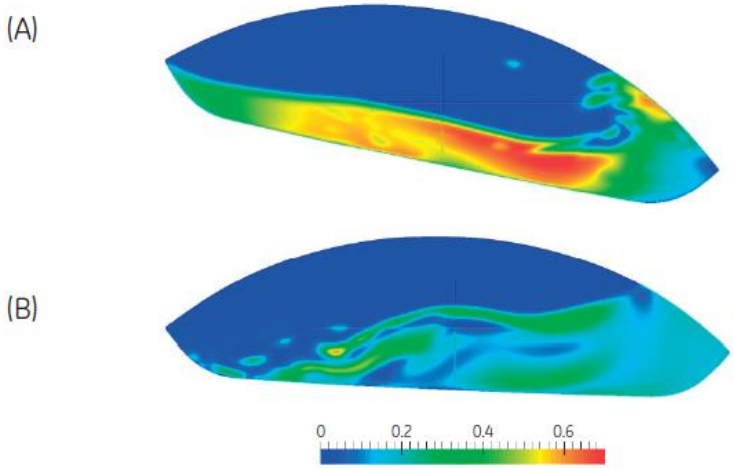
Advantages of a simple rocking bioreactor with the functionality of an advanced stirred-tank bioreactor

- Easy to set up and quick turnaround times
- Advanced controls functionality (pH, DO, perfusion)
- Programmable UNICORN™ Method Editor software enables further automation

Well-characterized engineering parameters simplifies process transfers

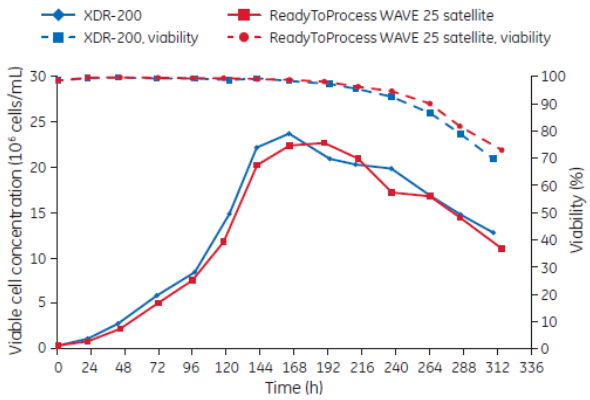


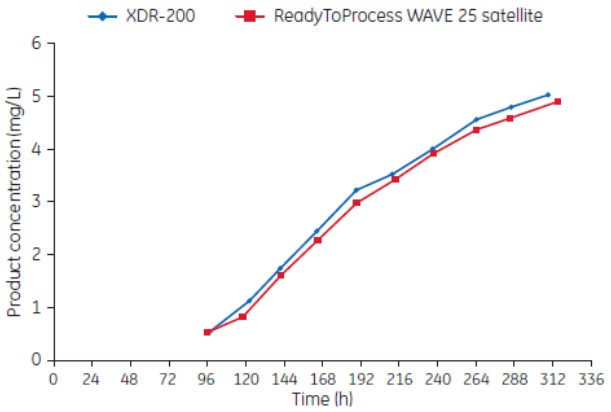


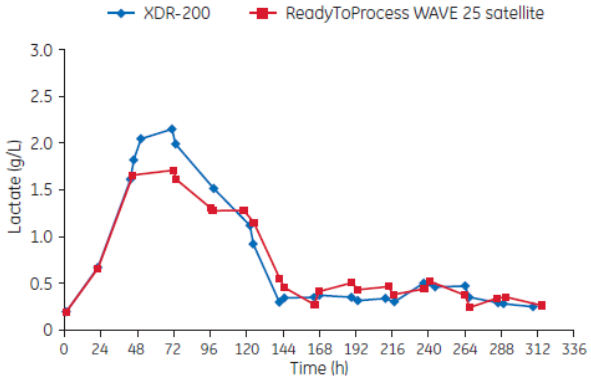


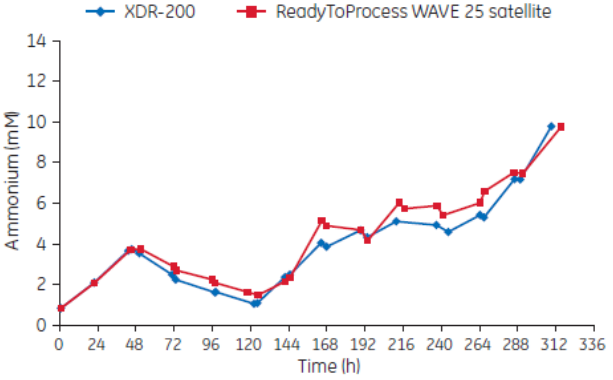
CFD-predicted fluid velocity magnitude pattern in the Cellbag culture chamber with 10 L filling volume at 40 rpm, 12°, and 100% acceleration. Contour plot of velocity magnitude on y–z-plane (side view) at (A) 19.05 s and (B) 19.45 s.

Comparable performance of high titer fed-batch culture in XDR-200 and WAVE 25





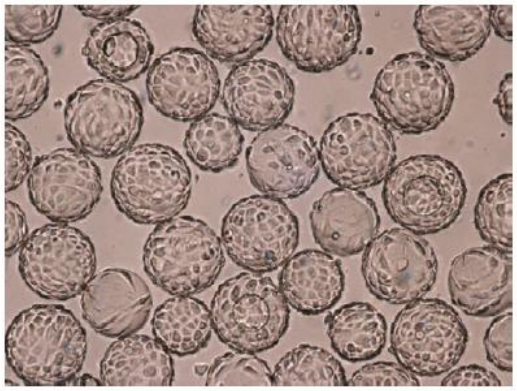




WAVE 25 can be used as scale-down model in PD for large-scale stirred-tank bioreactors

WAVE Bioreactor™ in adherent cell cultures

(A)



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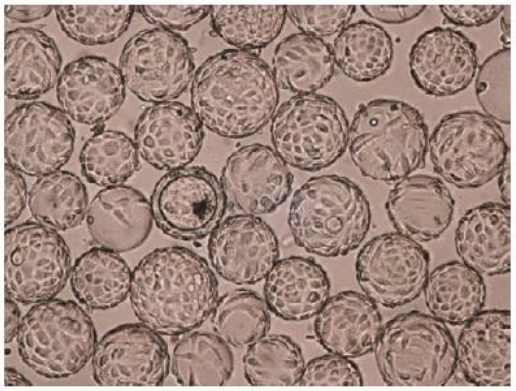
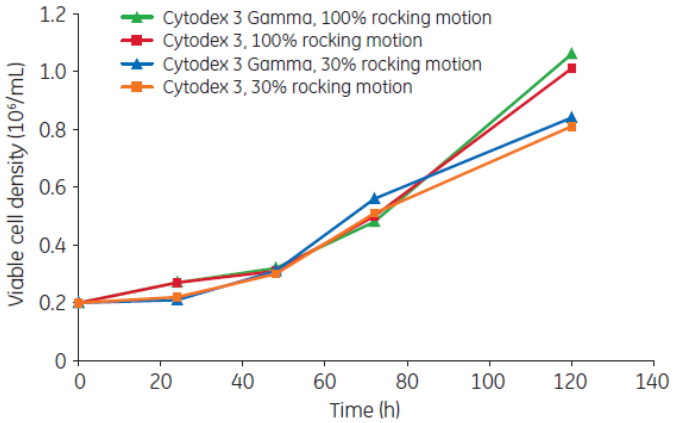


Morphology of Vero cells grown on (A) Cytodex™ 3 Gamma or (B) Cytodex 3 microcarriers 96 h after inoculation. Bioreactor culturing was conducted using a rocking motion setting of 100%.



Adjustable rocking motion facilitates culture of non-standard cell types

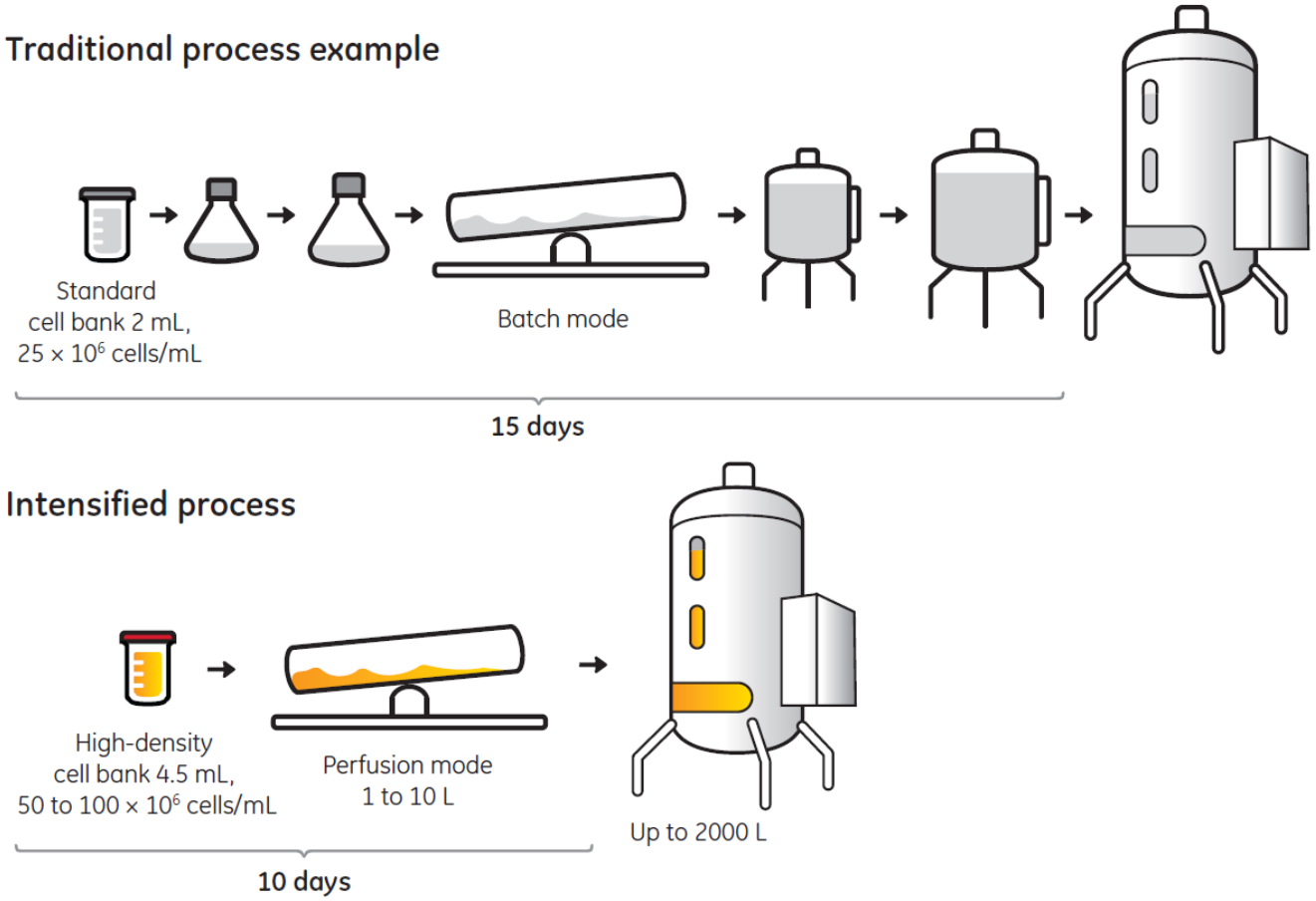
Conclusions

- Versatile, easy-to-operate capability with advanced physiochemical controls

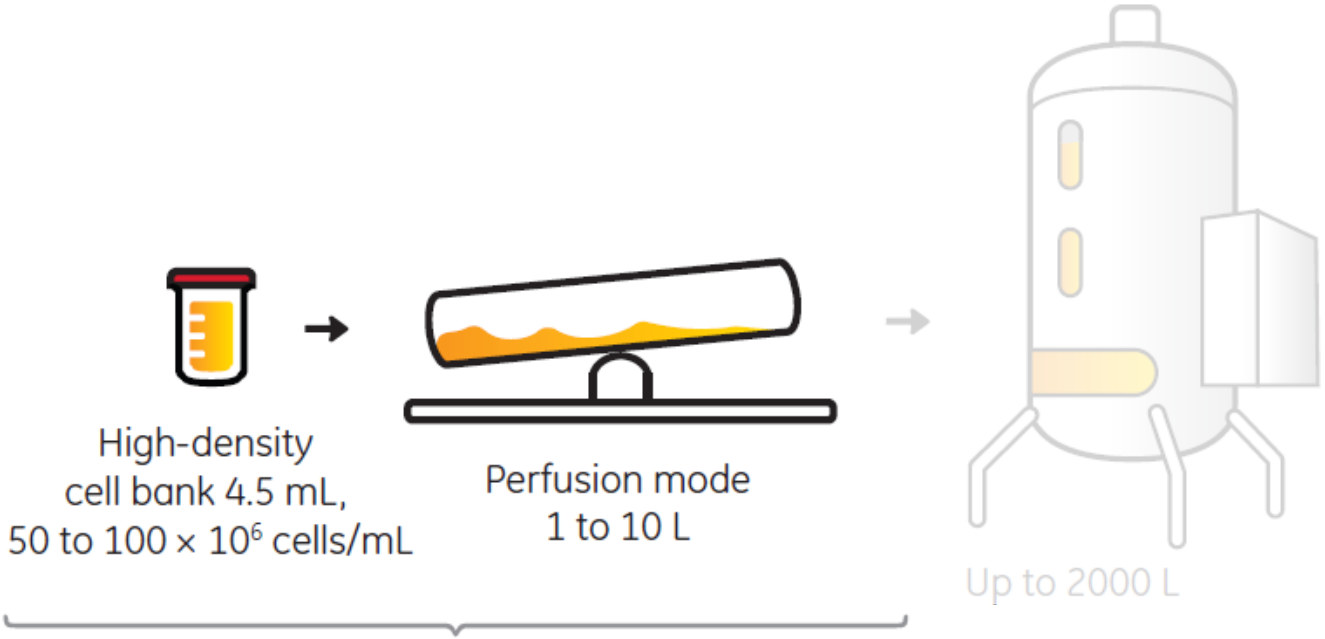
- New capabilities of WAVE 25 make it an attractive alternative to small-scale stirred-tank bioreactors in process development

Case study: an advanced one-step inoculum process

Process intensification though perfusion: for simplified cell banking and efficient scale-up



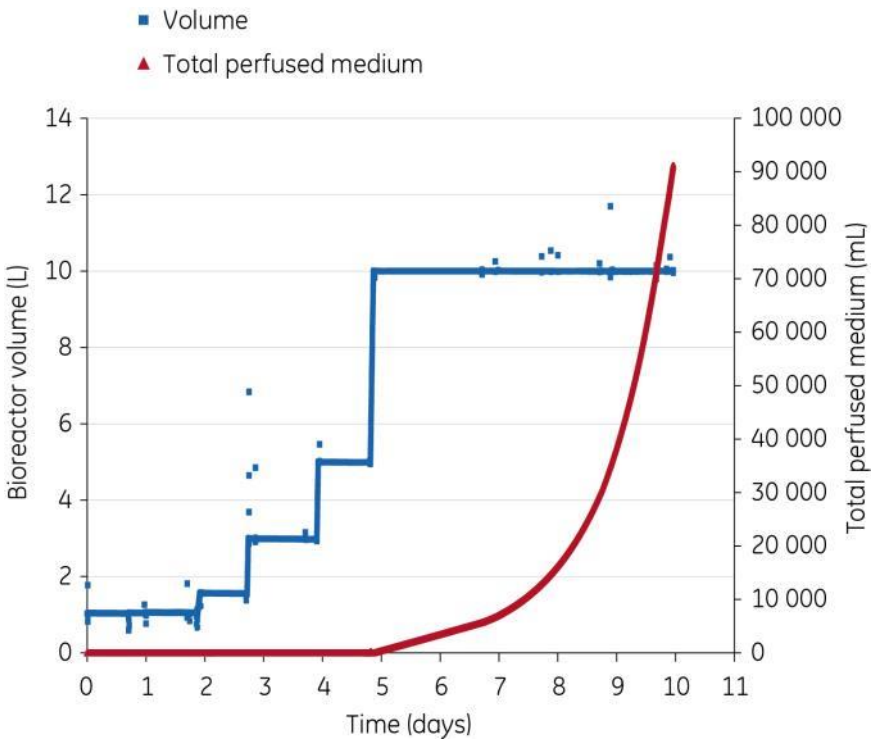
Experimental setup



ReadyToProcess WAVE™ 25 system setup for the perfusion process

- Single-use disposable bioreactor with internal perfusion filter
- Accurate process controls
  - Dissolved oxygen (DO)
  - pH
  - Continuous medium flow rates
  - Volume control
- Allows
  - High cell densities (> 100 × 10^6 cells/mL)
  - Increased levels of automation with UNICORN™ software Method Editor function

Culture conditions for seed expansion from 4.5 mL vial to 10 L perfusion culture

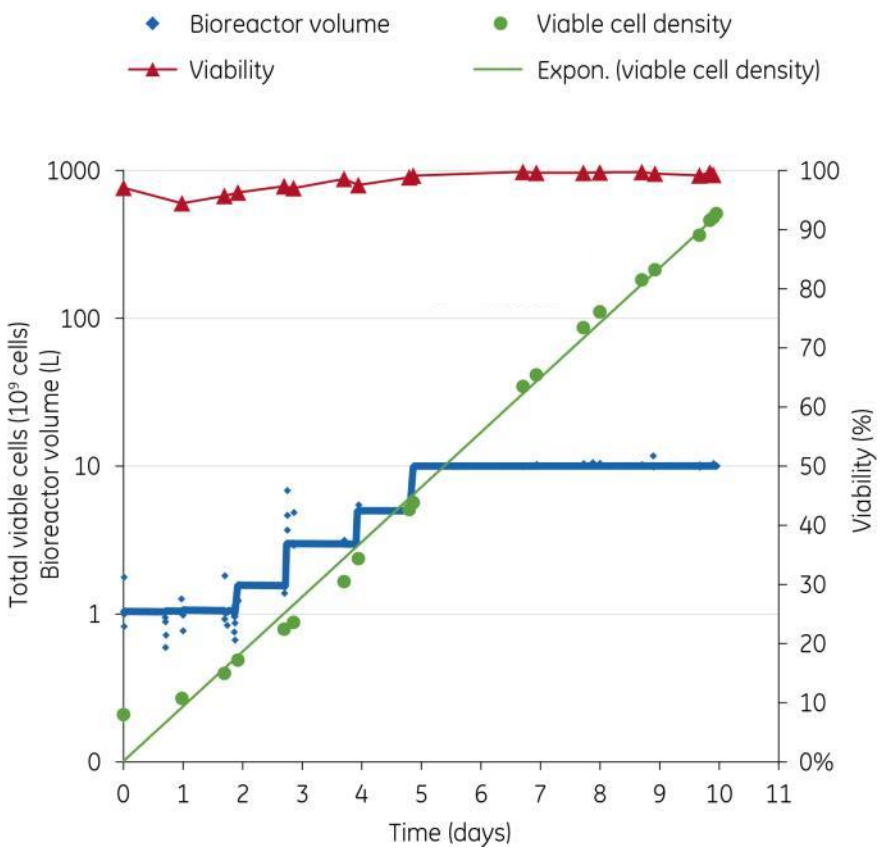


- Perfusion medium: ActiCHO™ P medium
- Working volume: 1 to 10 L (gradual automated daily volume expansion using UNICORN™ software)
- Set points: pH 7.1, 40% dissolved oxygen, 36.8°C culture temperature
- Perfusion rate: ~ 140 pL/cell/d

Target criteria:

- 50 to 100 × 10^6 viable cells/mL
- > 95% viability

Culture growth was exponential



- Average specific growth rate:
  - 0.96 day^{-1} from day 4 (doubling time ~ 20 h)
- Cell-specific perfusion rate:
  - 140 pL/cell/d from day 5
- Culture duration:
  - 10 days (5 + 5)
- At harvest:
  - Viable cell density: 51.2 × 10^6 cells/mL
  - Cell viability: > 95%

Summary: one-step seed culture process case study

- One 4.5 mL cryovial from cell bank was sufficient for direct inoculation of a 20 L bioreactor.
- Perfusion was used to increase the cell density in the bioreactor to > 50 × 10^6 cells/mL in 10 L.
- The entire growth phase could be performed in one bioreactor.
- Achieved cell density is sufficient for seeding of a 2000 L production bioreactor at a starting volume of 1700 L, for example.

FTE = full time equivalent

Entire inoculum process can be run with just one operator (< 1 FTE) and can be semi-automated

Impact of an intensified seed train strategy on process economy

Identified sources of cost savings with an intensified seed train strategy

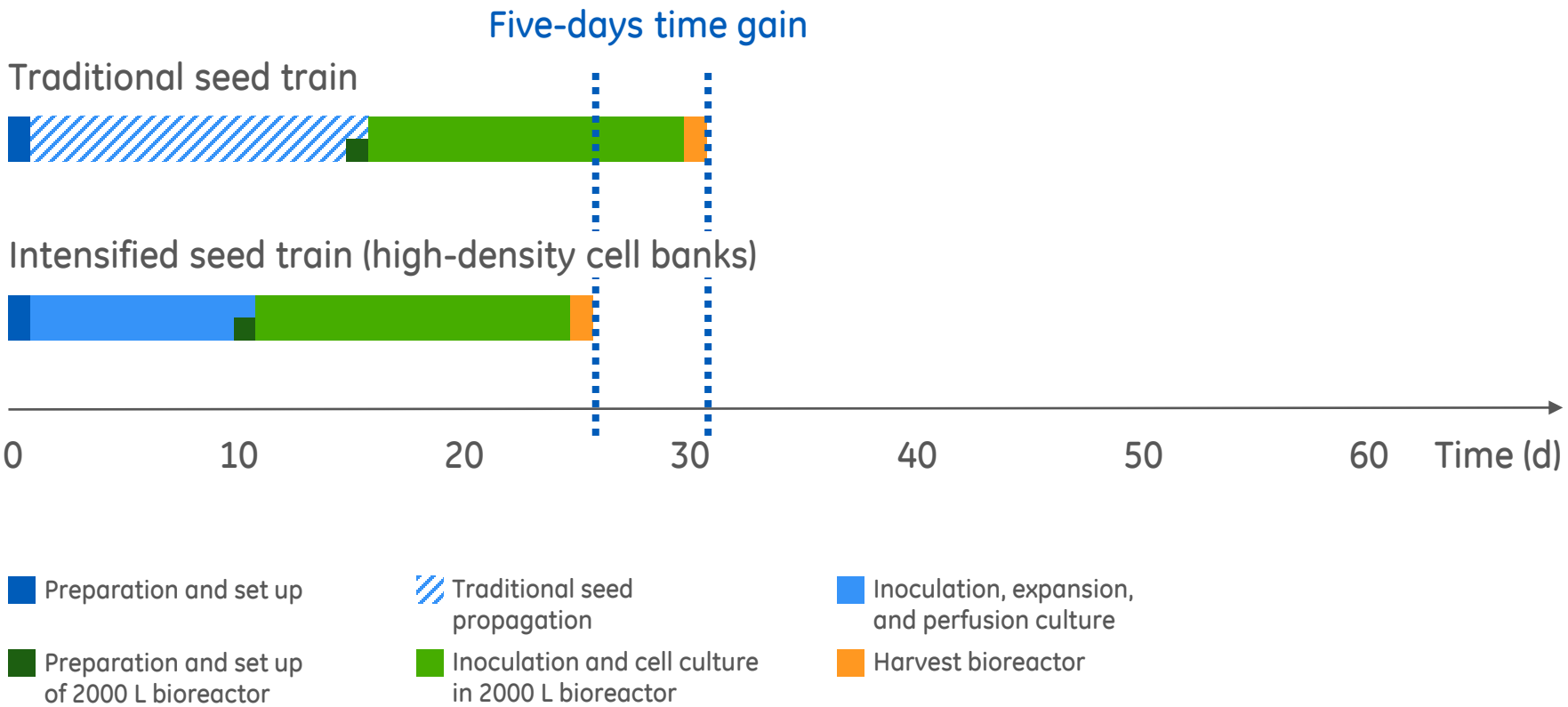
- A higher plant utilization in terms of batches produced per year
- A smaller facility footprint with fewer bioreactors
- Lower facility investment costs (equipment)
- Lower consumables costs
- A significant reduction of the labor required for seed preparation

Assumptions for process economy models

- Calculations on upstream process exclusively
- All operations in single-use format
- Both processes deliver the same number of cells to the production stage bioreactor
- Different scenarios for campaign length: one to five batches per campaign vs single-product facility
- Standardized values for equipment footprint, depreciation, and costs for facility, consumables, and full time equivalents (FTE) were used

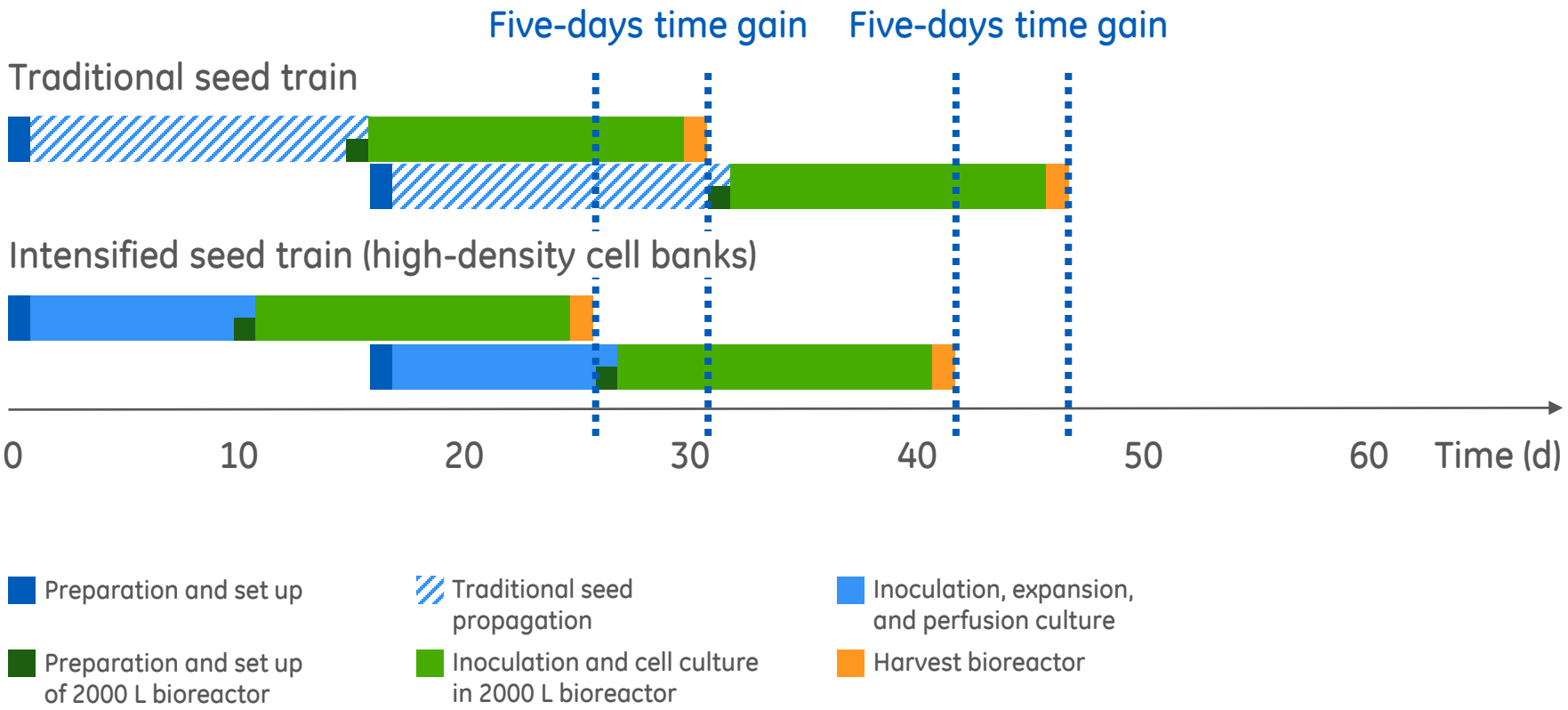
An intensified seed train strategy enables process time gains

Schedule example, one batch



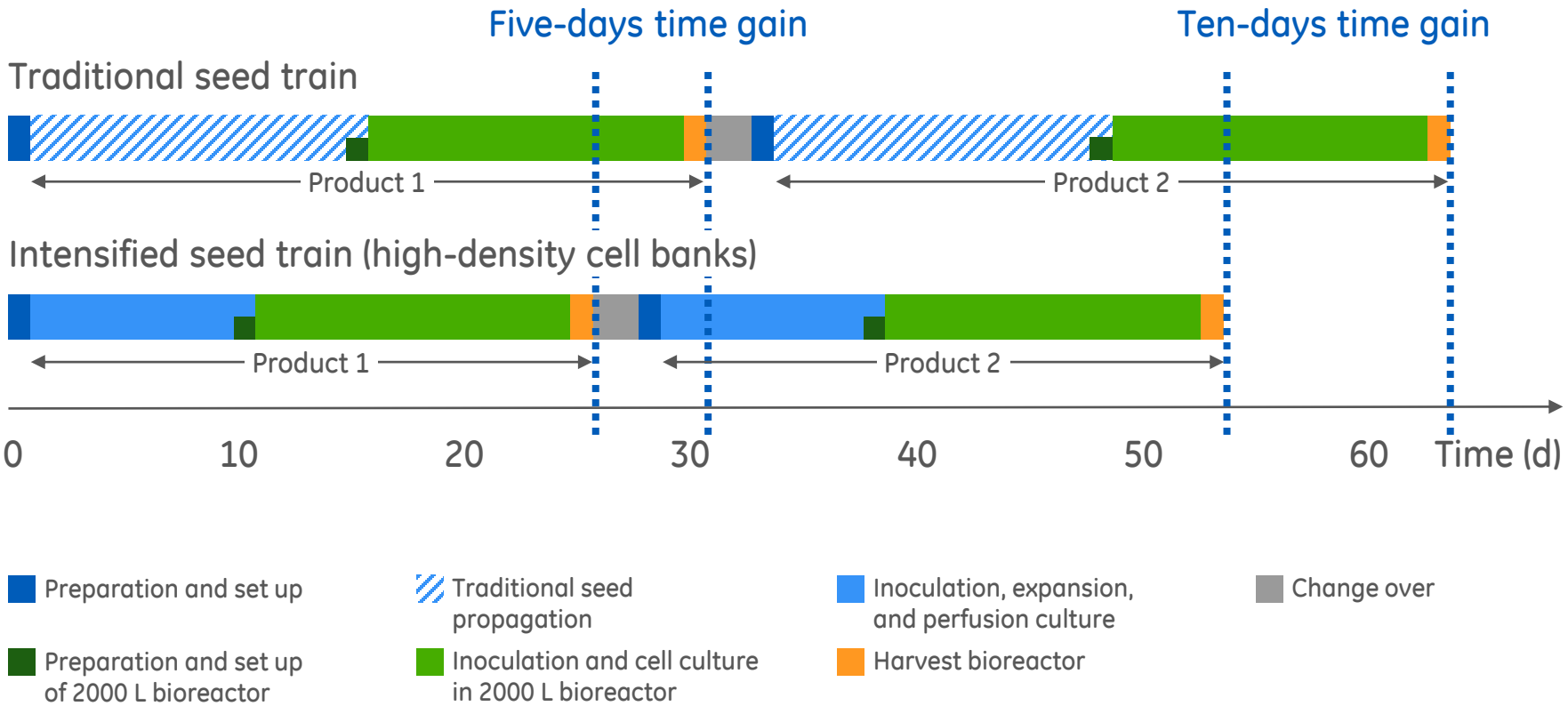
The time gain can be leveraged every time a new batch is started

Schedule example for a single-product facility, two batches

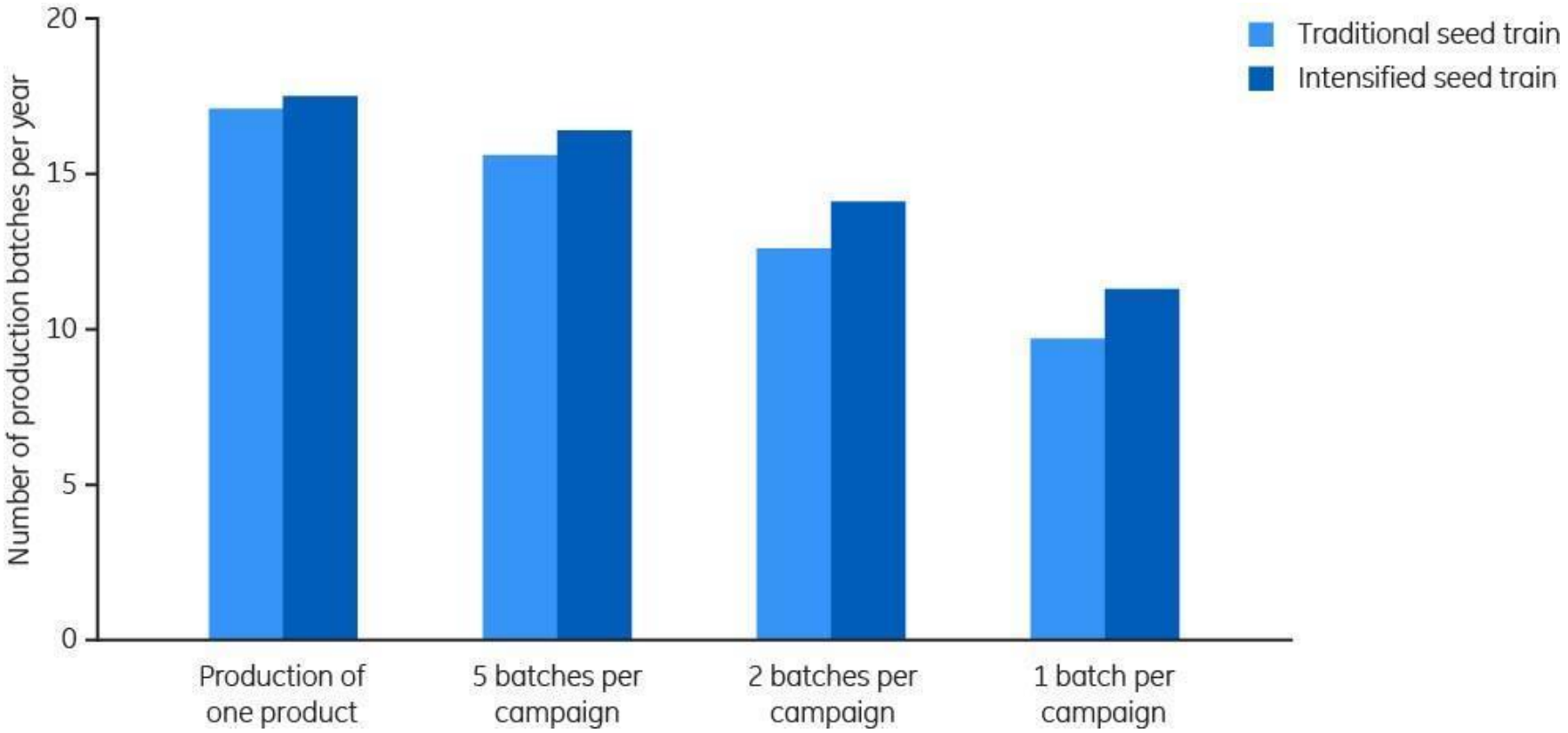


For multi-purpose facilities, the time gain increases with each new campaign

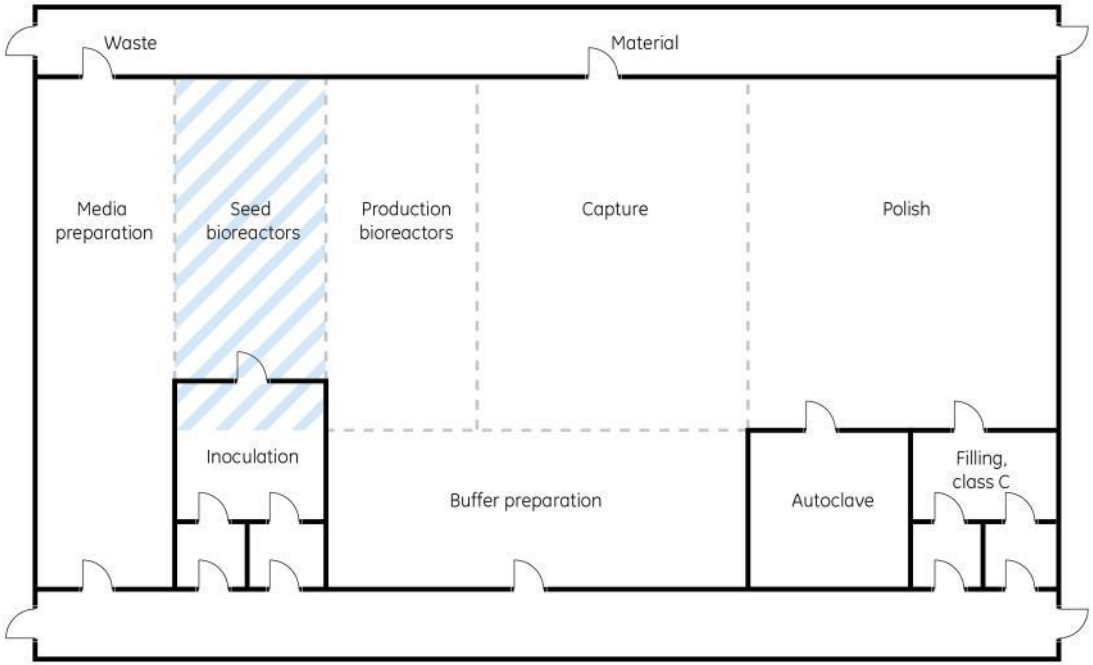
Schedule example for a multi-purpose facility, two products



A higher number of batches per year can be produced with an intensified seed train strategy

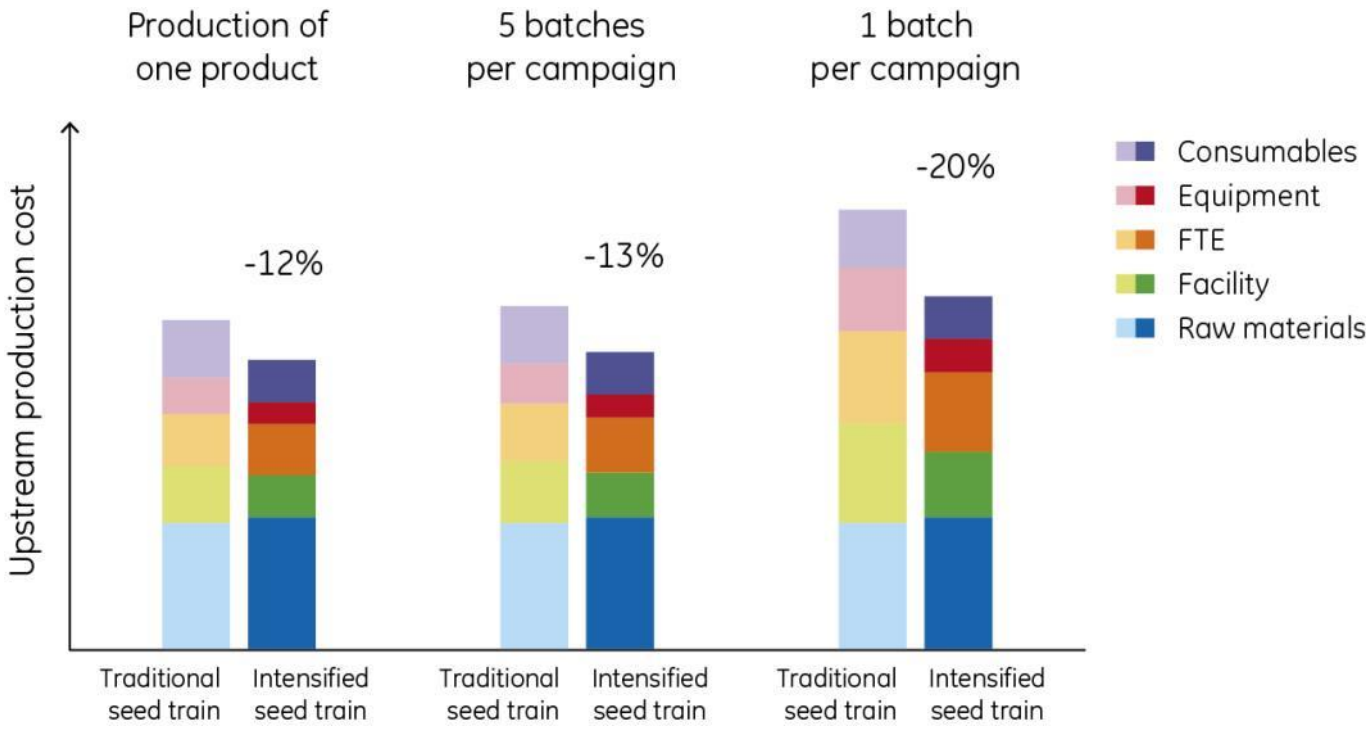


Impact on facility footprint



Opportunity to decrease facility footprint by 60 m^2 with a high-density seed expansion strategy

Cost savings enabled using an intensified seed train strategy



Highest gain with small volume products with few batches per year produced

Several process gains enabled through a high-density seed expansion strategy

Compared with a traditional approach, the presented high-density seed expansion strategy enabled

- Up to two batches more produced per year through a higher plant utilization
- About 60 m^2 reduction in facility footprint with fewer bioreactors
- About 40% reduction of labor time for seed preparation
- Between 10% and 20% reduction in upstream production cost

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GE Healthcare Bio-Sciences AB
Björkgatan 30
751 84 Uppsala
Sweden

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