Strategies for Upstream Intensification

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The Facility of the Future represents a transformation in how biologics are developed and manufactured. Upstream intensification is one strategy that will enable this revolution by significantly driving down costs through an increase in volumetric productivity. (Figure 1).

In addition to increasing productivity, upstream process intensification has the potential to accelerate protein production and increase protein quality. Perfusion-based strategies are increasingly leveraged for this intensification as they deliver speed, productivity, flexibility and reliability. These strategies can be applied to cell line development, seed train, production and cell culture media formulation (Figure 2).

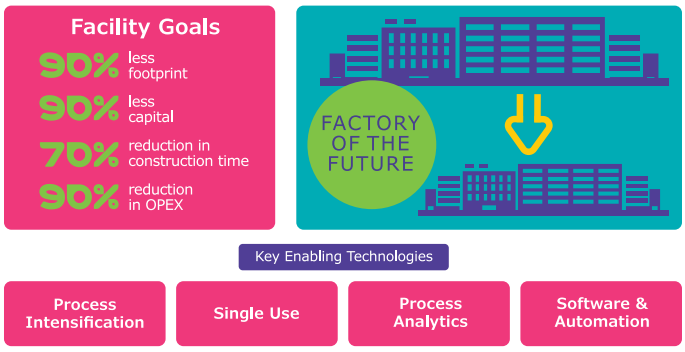

Figure 1. The industry expects to significantly reduce manufacturing and capital costs with process intensification (Adapted from BPOG Technology Roadmap, 2017).

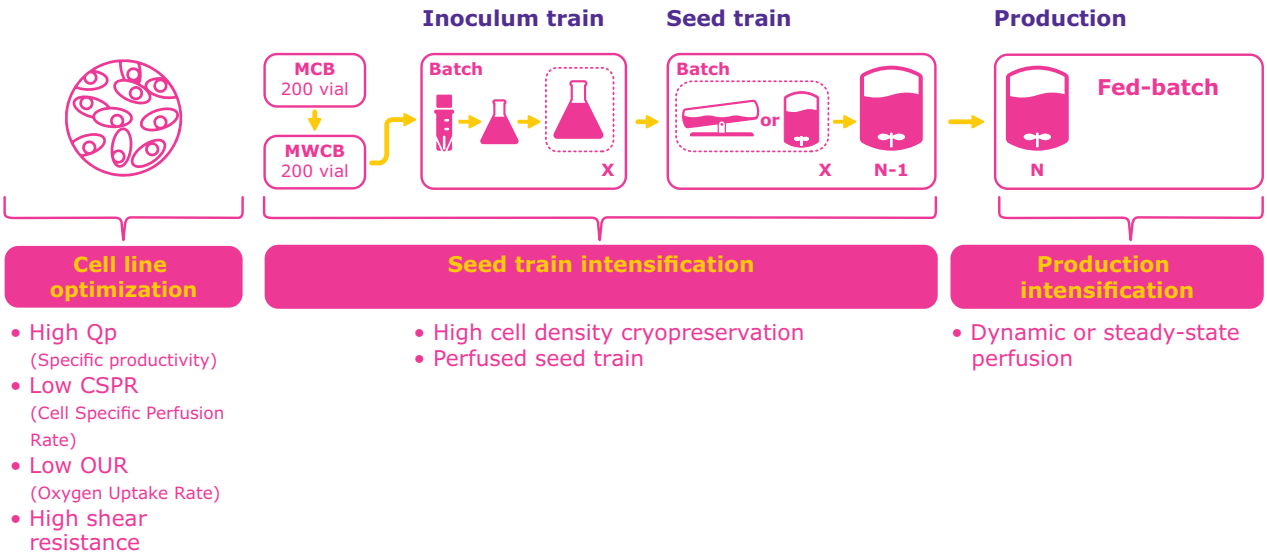

Figure 2. Strategies for upstream process intensification can be leveraged for cell line development, the seed train, production and cell culture media formulation.

Streamlining Seed Trains with High Cell Density Cryopreservation (HCDC)

Thawing a single vial of cells to initiate cell expansion for a GMP manufacturing batch is time-consuming and requires open cell culture operations. Use of HCDC method, which feeds into the first seed train bioreactor, can streamline the overall process by up to 10 days[2] (Figure 3).

As the frozen volume is relatively high, single-use bags are more appropriate than vials, allowing HCDC to be used in closed processing, reducing contamination risks.

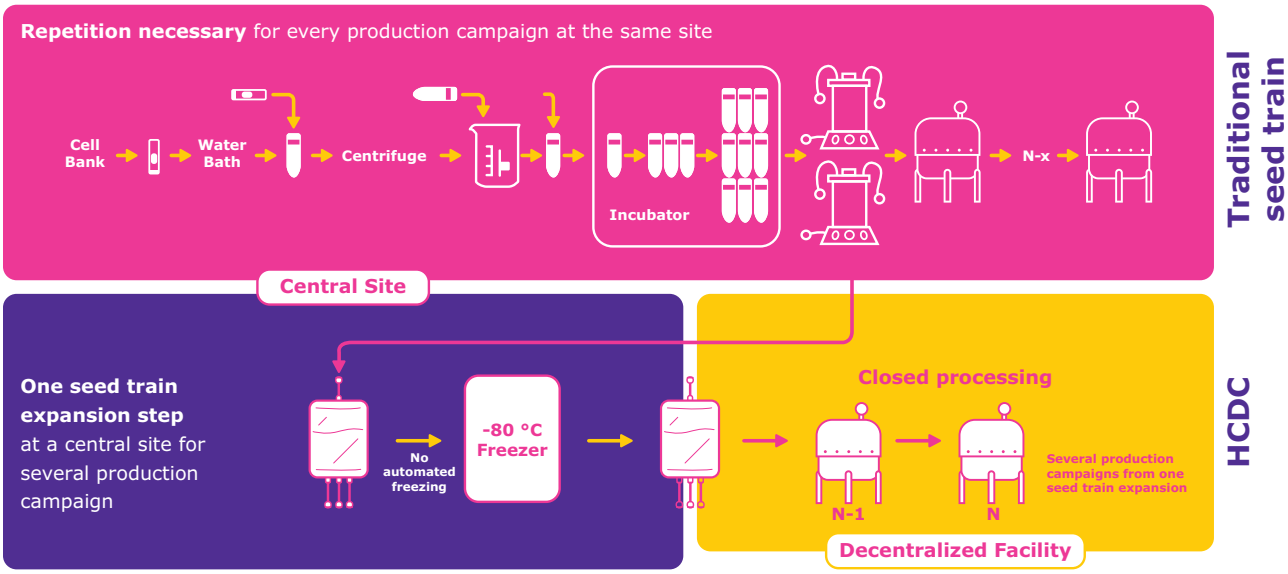

Figure 3. HCDC enables one seed train expansion step at a central site in support of several production campaigns.

Significantly Improving Process Economics with a Perfused Seed Train

Perfusion-based processes, especially in the seed train, can reduce the costs of manufacturing and increase product throughput, all while maintaining the production bioreactor in a more simple-to-operate fed-batch mode.[1]

In addition, perfused seed trains allow for high seeding of the production bioreactor, which can potentially enable an increase in titer, especially when incorporating a robust media platform (Figure 4 and 5).

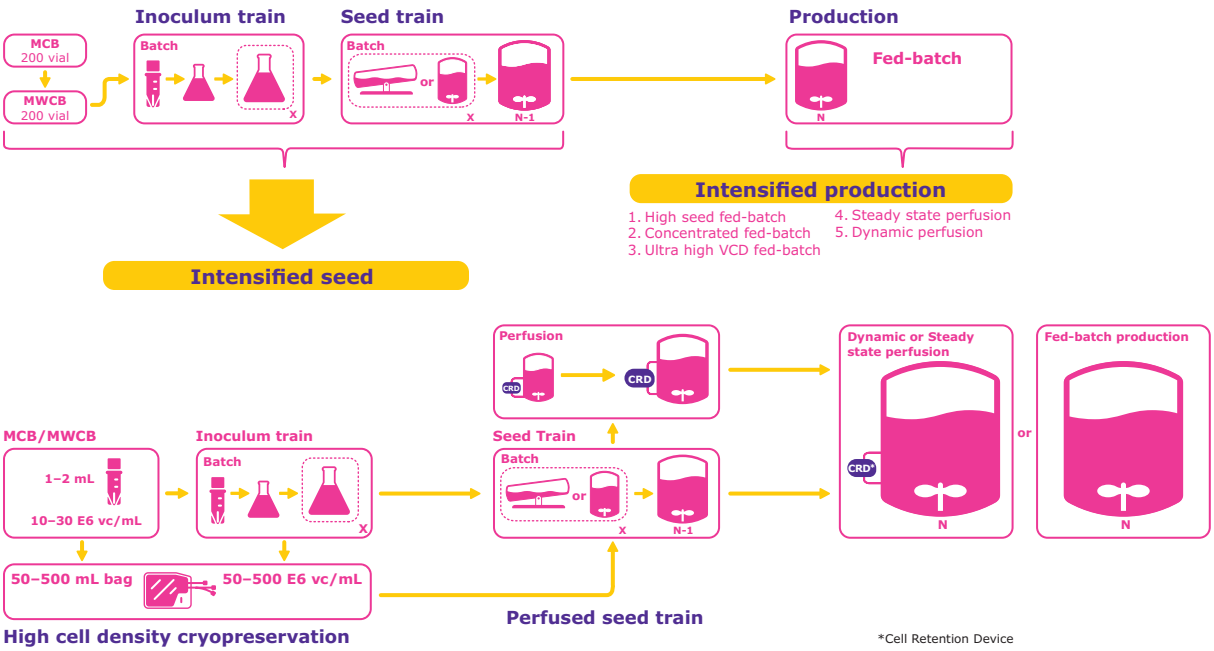

Figure 4. Upstream intensification approaches such as perfusion and HCDC can improve process economics.

Achieving High Cell Densities and Productivity with Specially Designed Media Platform

Specially designed cell culture media for perfused seed train cell expansion allow for spiking the production bioreactor with higher cell densities. Additionally, use of specially designed media platform across the workflow, from cell bank to production, also creates a consistent environment for cells. This minimizes the time needed for cell adaptation during transfers from the cryobank to expansion and production (Figure 5).

Each formulation in the media platform has a specific role and must be compatible with each other in order to minimize adaptation when transferring cells from one step to the next:

- Cryomedium must support freezing and thawing of cells without cell damage.
- Expansion medium must have a high nutrient concentration to achieve low cell specific perfusion rates (CSPRs) at high cell densities, enabling greater seed train process efficiencies.
- Perfusion medium must facilitate high productivity at low perfusion rates.

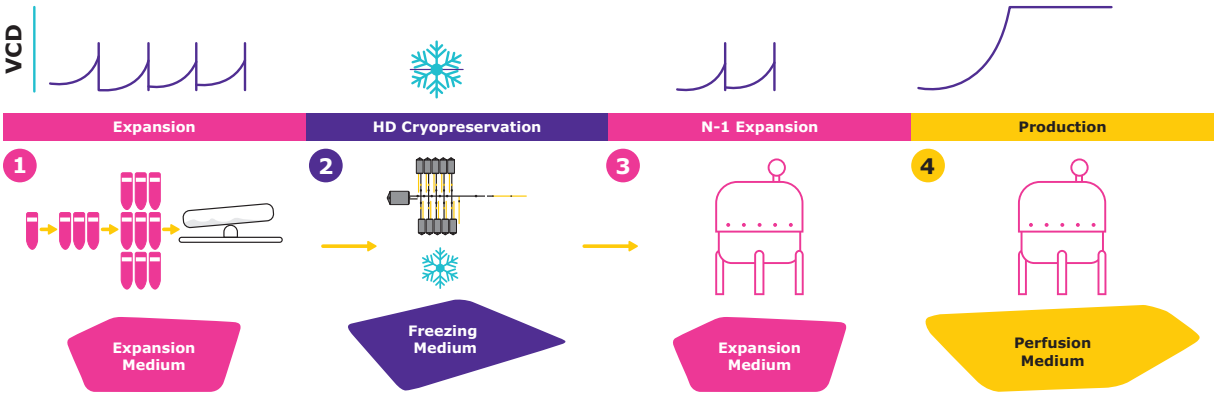

Figure 5. Media designed for upstream intensification support the overall upstream process.

Getting the Most out of Perfusion Culture with Cell Retention Devices

An essential component for reducing the risk and complexity of perfusion culture is a cell-retention device that allows for high cell density and a wide range of media exchange rates, with minimal fouling and reproducible performance (Figure 6). Our cell retention device includes a flat-sheet membrane-based technology, optimized to ensure performance, scalability and eliminate any potential negative impact on cell health. Use of this technology results in greater cell-mass production in the N-1 bioreactor allowing your production bioreactor to be seeded at a higher cell density. This higher cell inoculation density eliminates any lag phase resulting in a shorter time required to reach peak cell density and achieving higher titers[3].

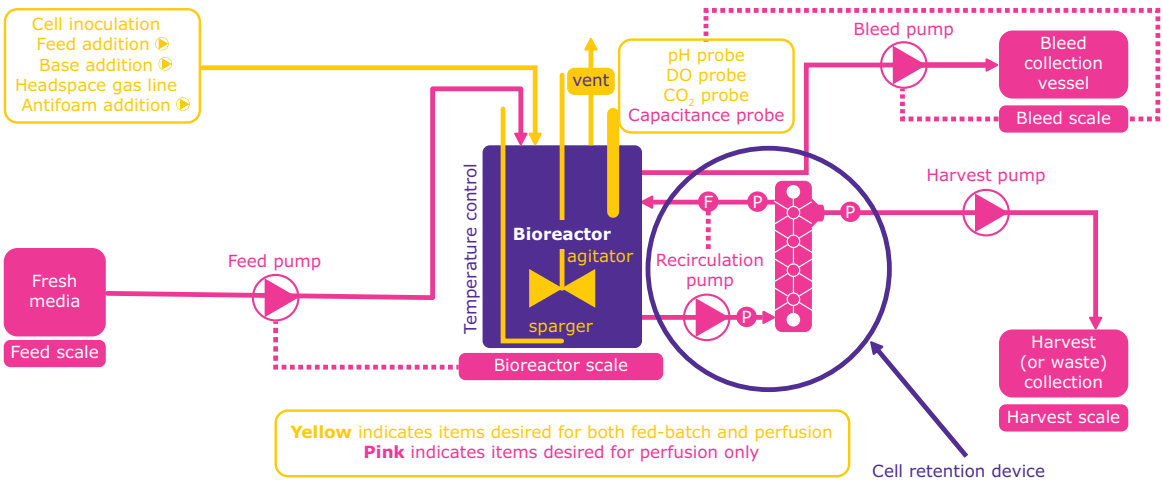

Figure 6. A cell retention device is critical to derive the greatest benefit from perfusion approaches.

Webinars

1. A Cost analysis and evaluation of perfused seed train scenarios through process modeling

Utilization of process modeling to quantify the benefits of perfused seed trains, and to determine under which scenarios these benefits arise.

2. Media and process development for seed train intensification

Demonstration of how combining media, specially designed for seed train, production and harvest intensification, can increase the cell specific productivity (Qp) in the final production stage.

3. Novel Perfusion Filter and Controller for N-1 Application

A study comparing a control process to the use of tangential flow filtration in the seed train and evaluating various process parameters.

EMDMillipore.com/webinar

Looking to intensifying upstream? Find the the right products

Retention device	Specially designed cell culture media for expansion	Specially designed cell culture media for perfusion
Cellicon™ Perfusion Filter and Controller	**Cellvento® 4CHO-X Expansion Medium**	**EX-CELL® Advanced HD Perfusion Medium**
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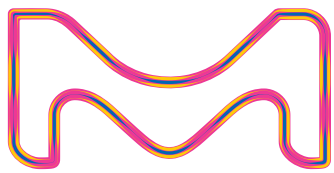

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