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Key Trends Reshaping The Future of Bio-pharmaceutical Harvest & Clarification

Frost & Sullivan Executive Brief

Cell harvesting and clarifications are both crucial steps that can have a significant impact on the design of downstream processes. Briefly, the primary goals for harvest and clarification (H & C) operations are to remove cells and cell debris from mammalian cell culture and further purify and clarify the resulting product to capture the mAbs via chromatography downstream.

IMPACT OF PROCESS INTERDEPENDENCIES

As processes change upstream in the pharmaceutical manufacturing workflow, causing variability of cell culture fluid, downstream purification unit operations will be impacted.

Variable cell culture fluid creates a range of negative effects on downstream purification including decreasing overall yield, antibody degradation, and aggregation. Often the variability may not be seen in a single drug product, but instead across a company's entire drug portfolio, which requires multiple manufacturing platforms or facilities.

Also, not all components of the cell culture fluid are completely removed by a single unit operation. The combination of the insoluble cells and cell debris (for example, mammalian, insect cells, bacteria and plant) and the cell culture soluble components (for example, host cell and product proteins, hot cell DNA, buffers, anti-foams, and cell culture media) can cause challenges with established clarification technologies, when the success metric is defined as consistent fluid quality for downstream purification.

With the industry moving toward higher titers, a key challenge in cell harvesting is how to deal with higher cell densities. The higher titers and densities have created growth opportunities for filtration technologies that can handle the large amounts of cell mass.

By mapping these different process inter-dependencies, H & C operations can be sized to build an optimized scheme without wasted capacity and without incurring additional costs.

DESIGN CHALLENGES IN HARVEST & CLARIFICATION

Processes developed only for early stage drug development may fall short on yield and throughput and are not entirely suitable for producing the large quantities required in late-stage commercial settings. Once the candidate antibody has passed the hurdles of early stage clinical studies, a more optimal process that takes these additional factors into account may need to be developed.

Furthermore, a major unmet need within harvest unit operations is an ideal clarification strategy that results in invariant conditioning of fluid for subsequent purification operations including chromatography. While flocculation and precipitation are strategies that have been employed for this purpose, unmet needs still remain including the development of an ideal universal solution that can be employed across various scales and molecule types.

Over the past decade, most biopharmaceutical companies have addressed challenges in H & C by taking a proactive approach to mapping end-to-end workflows and tightly defining success outcomes.

Most companies generate detailed feedstock characteristics (nature of protein, etc.) and volume (filter capacity targets, etc.) to set targets on yield, impurity removal level and processing time.

LIMITATIONS OF CURRENT HARVEST & CLARIFICATION TECHNOLOGIES

A key goal for the process developer is to achieve the highest level of product recovery and contaminant removal with the fewest number of unit processes.

Let's imagine that a manufacturer is aiming for ten grams per liter product protein concentration out of the bioreactor, with cell densities greater than twenty million cells per milliliter. Concurrently, cell viability at the time of clarification has generally decreased to less than fifty percent. For this scenario, the increased cell debris and colloid content (due to lower cell viability) has led to decreases in sterile microfiltration membrane life.

To manage these fluid conditions, the manufacturer considered tangential flow microfiltration (TFF-MF for short) to increase the microfiltration membrane life.

However, this harvest technology displayed several shortcomings such as reproducibility, and reduction in capacity.

Even though TFF–MF processes are often designed to minimize the rupture and fragmentation of cells in the recirculation loop, the high cell density fluids result in increased cell shear and fragmentation. As a result, a secondary clarification depth filter may be required after TFF-MF to reduce the small-particle load before sterile microfiltration.

Although multiple linked stages are common within harvest and clarification to achieve product clarity, each unit operation increases the potential for additional product yield loss.

Finally, improved titers present facility fit challenges in legacy chromatography architecture with capacities originally matched to lower titers.

NEW HARVEST AND CLARIFICATION STRATEGIES (ENABLING OVERALL PROCESS ROBUSTNESS)

To develop an efficient harvest and clarification process, a dynamic approach based on new technologies that facilitate robust integration of multiple steps is needed.

Single-use centrifugation, depth filtration, sonication and flocculants or body feed-based unit operations may reduce the contaminant load and help generate higher purity harvest. Depth filtration and membrane (sterile) filtration facilitate further removal of debris, while chromatography filters permit a cleaner Protein A elutant.

These solutions may enable optimization unit processes and deliver filtration consistency to protect downstream unit operations while reducing operating costs.

HIGH-PERFORMANCE FILTRATION THAT UNLOCKS NEW H&C DESIGN ARCHITECTURE

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- 3m.com/bioprocessing
- 3M™ Zeta Plus™ EZP Series
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- A Frost & Sullivan Perspective on Next Generation Harvest and Clarification Techniques

NEXT STEPS

- **Schedule a meeting with our global team** to experience our thought leadership and to integrate your ideas, opportunities and challenges into the discussion.
- Interested in learning more about the topics covered in this white paper? Call us at 877.GoFrost and reference the paper you're interested in. We'll have an analyst get in touch with you.
- Visit our **Transformational Health** web page.
- Attend one of our **Growth Innovation & Leadership (GIL)** events to unearth hidden growth opportunities.

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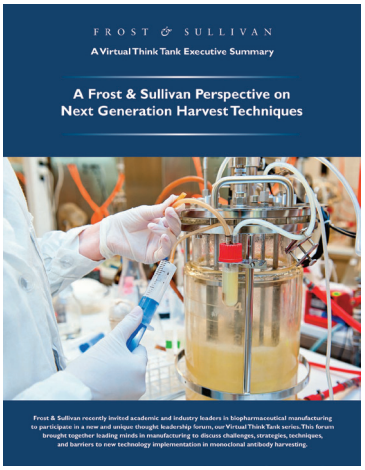
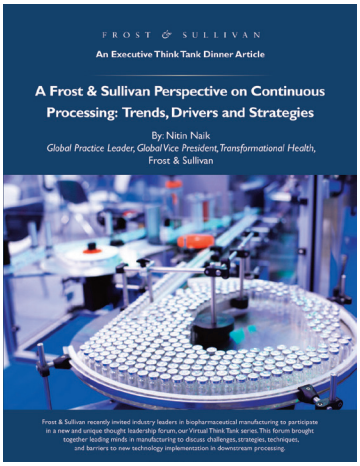


Perspective on Next Generation Harvest Techniques

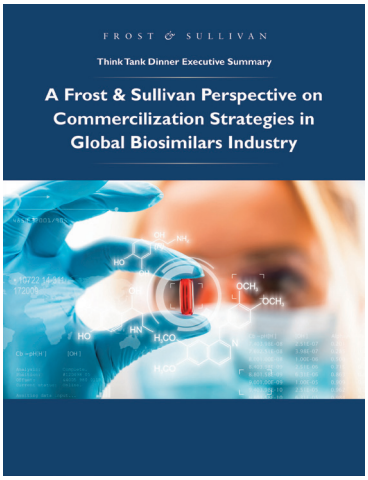
Transition to Next Gen Down-stream Processing to Capitalize on Growth Opportunities in High-Value Low-Volume Biologics

Enabling Novel Bioprocessing Technologies Using the Interface of Materials Science Biotechnology



Perspective on Continuous Processing: Trends, Drivers and Strategies

Cell Therapy Biomanufacturing: Trends and Perspectives



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