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A Virtual Think Tank Executive Summary

A Frost & Sullivan Perspective on Next Generation Harvest Techniques

Frost & Sullivan recently invited academic and industry leaders in biopharmaceutical manufacturing to participate in a new and unique thought leadership forum, our Virtual Think Tank series. This forum brought together leading minds in manufacturing to discuss challenges, strategies, techniques, and barriers to new technology implementation in monoclonal antibody harvesting.

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Challenges in Harvesting Necessitate New Technologies

The class of monoclonal antibody (mAb) therapeutics has grown considerably in the last two decades and now makes up a significant portion of the biotherapeutics market. With more than 70 monoclonal antibody drugs on the market, and 33 of those drugs launched between 2014 and 2017, pharmaceutical manufacturing operations continue to adjust to the new demand, particularly around the processes of harvest, clarification, and purification of mAbs.

Briefly, the primary goals for harvest and clarification operations are to remove cells and cell debris from mammalian cell culture, and further purify and clarify the resulting product in order to capture the mAbs via chromatography downstream. Traditionally, various technologies are used for these processes, such as centrifugation, microfiltration, depth filtration, and flocculants. However, new cell culture techniques, increased demand for monoclonal therapeutics, and a convergence of other factors in biopharmaceutical manufacturing has prompted the need for novel harvest and clarification techniques and technologies to increase the efficiency of the upstream and downstream processes for mAb production.

Several challenges in current harvest operations are necessitating changes in techniques and technologies. Newer techniques in mammalian cell culture, a result of increased demand for mAb therapeutics, have impacted the conditions for cell harvesting. Xiaoyang Zhang, Principal Scientist at Amgen, described that "One of the trends in cell culture, perfusion cell culture, means the process is smaller scale and continuous, but it also means very, very high cell density." A recent publication by MedImmune announced that the company was able to culture a very high density 120 million cells per mL, which posed a huge challenge to conventional harvest technology. Echoing this, Nripen Singh, Associate Director, MS&T Downstream at Bristol Myers Squibb, described the push to move away from conventional centrifugation given its ineffectiveness with increasing cell biomass, high cell densities, and high titres stemming from these new cell culture processes. Additionally, the high capital cost and significant maintenance and cleaning required for centrifugation makes the technology a prime target for replacement with

novel technologies. The changing cell features are driving not only changes in clarification, but also purification, making this trend very challenging across the manufacturing workflow. Singh suggested the employment of single-use, disposable technologies as a way to avoid the pitfalls of centrifugation, especially for low volume products.

From a different perspective, Brian Kluck, Research Scientist at Gilead Sciences who works on early stage Phase I clinical production, described being, "primarily challenged with the scale-dependent harvest processes" with technologies varying by the phase of drug development, and thus the scale required. Development, pilot, clinical, and commercial scales all have different harvest processes, which Kluck described, "results in highly variable impurity levels, making scale-down model qualification difficult and optimization around some Phase I development very challenging by not having a consistent or robust impurity profile to develop around." Kluck suggests that technologies that are universal across scale could help normalize and create consistency across drug development phases.

Alexei Voloshin, Global Application Strategy Specialist at 3M, echoed the need for scalable, predictive technologies that result in higher yield to be implemented. He explained, "Two primary challenges have been identified. One is scalability, which means having predictive technologies at smaller scale that can linearly scale up to clinical and then commercial manufacturing scales. Second is yield, so the ability to have a platform process where all across your candidate pipeline at different modalities, you get yield that is completely predictable and also high."

Furthermore, a major unmet need within harvest unit operations is an ideal clarification strategy that results in invariant conditioning of fluid for harvest. While flocculation and precipitation are strategies being 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.

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Katherine Fong said, "I think one of the challenges right now is that we do not have a stand-alone technology that is capable of conditioning a fluid without a perceived impact on the product quality." To overcome these current unmet needs, some companies are performing a combination of techniques to achieve the desired outcome.

Jean Bender, VP Pharmaceutical Sciences and Technology at Visterra, commented, "While these techniques are not new, people have tried varying degrees of flocculation and/or precipitation in order to improve the separation efficiency with the centrifuge. Conditioning the fluid or providing some sort of purification as part of harvest has been a challenge along the way as the cell density is increased. The methods may not be a universal solution, but labs may utilize a combination of flocculation and centrifugation, or flocculation and some of these newer technologies coming out."

Impacts on Downstream Units

As processes change upstream in the pharmaceutical manufacturing workflow causing variability of cell culture fluid, downstream purification unit operations will be impacted. After the harvest process, purification processes remove impurities, such as aggregates, DNA, endogenous/adventitious viruses, host cell protein, endotoxins, and other unwanted material. Additional steps purify any material introduced to perform the purification, such as resins, filters, buffers, leached Protein A from chromatography, and detergents. Variable cell culture fluid creates a range of negative impacts on downstream purification, including effects on titre, yield, antibody degradation, pH range variability, and overall product quality.

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> Visterra

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. Bender explained, "I see variability in titre across product platforms. In the same facility, you might be expected to do purification with processes that deliver 2 grams per liter and 5 grams per liter. You cannot equally do those well depending on the equipment, the system, and the time." Additionally, product robustness of the intact monoclonal antibody can vary due to upstream cell culture fluid, for instance if the fluid has a very high concentration of aggregates. Bender continued, "Then there is an impact on performance if you need much tighter elution conditions which sacrifices yield, and you may also have a molecule that is not as stable at varying pH levels."

One way to ease some of the negative impacts on downstream purification processes, according to Kluck, s to use technologies that could, "enable potential impurity clearance validation of the harvest filtration step, which could provide a consistent impurity input into the downstream process." Kluck suggested that the traditional DE based depth filters used in harvest processes ma no longer be sufficient for upstream clarification, but rather new solutions should start to look more like chromatography. Voloshin agreed, stating "What we like in purification processes is the reproducibility of chromatography. Every single time, assuming you get an input which is relatively consistent, you get an adequately consistent output." Alternatively, filtration depends on the pressure being applied, and whether impurities are being captured on the membrane or being extruded through the membrane. These uncertainties can product variable results, which is conflicting with the increasing demand for reproducibility in these unit operations as processes become intensified.

Ultimately, the impact of cell culture fluid variability on downstream purification really depends on the product, whether biosimilar or innovative, or small or large volume. Zhang explained that with biosimilars, you must match the existing reference product profile, which means it has higher requirements. If the company develops its own innovative, proprietary product now moving into manufacturing, the company conducts its own clinical trial to establish the profile, so it is not meeting the requirements set by another company. Therefore, Zhang concluded, "The cell culture variability can be more impactful for a biosimilar process than an innovative process."

Driver and Barriers to Implementation of New Technologies

Certainly there is a call for next generation harvest technologies and techniques to solve the various challenges presented to both upstream and downstream processes in drug manufacturing resulting from increased mAb production. However, changes in manufacturing workflows do not occur overnight, as implementing new processes and technologies into commercial scale operations requires extensive validation to ensure performance, time, quality, yield, and other metrics do not suffer. Furthermore, implementation requires intricate planning, often across multiple manufacturing sites, so as not to disrupt the supply chain. Yet implementation of new technologies is more likely to occur with new drug products than existing products already at manufacturing scale.

Nevertheless, many drivers exist to implementing new technologies, such as making the process scalable, reducing the technology footprint, reducing buffer consumption, and making continuous manufacturing possible.

Singh sees scalability as a major driver, stating, "One of the biggest drivers for us is to have a platform that can be optimized across the molecule and across the sites for a range of cell densities, anywhere from 20 million to 50 million cells per ml. We have not seen any new technologies that actually scale up from lab scale to full scale very well. So there would be quite a desire to have something which you can scale down and then predict your performance at a bigger scale." Jean Bender echoed that sentiment when speaking on added upstream clarification techniques, stating, "You're inviting additional process development work that can

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be helpful, but may not be extendable to the entire platform of molecules. There is a need to be able to improve these steps across the entire platform of molecules with as little development as possible."

With so many drivers to new technologies, it might seem like change is inevitable. However, the experts cautioned that need and ROI must be there to justify changes. Kenney suggested, "I think the biggest driver is always need; that the old ways just don't work anymore. These innovative new molecules need innovative new upstream techniques. I think there are a lot of barriers to push back new technology, like new costs and regulatory issues. So the number one thing that's going to push implementation forward is just the need to do it." Fong agreed, stating that risk aversion often means new technology must be justifiable with a significant ROI. Even if a new technology comes with an eventual cost saving, it must be upwards of 40% to justify the cost of implementing the new technology, which can be very high.

Prioritization of Innovation Efforts

Prioritizing where new processes and technologies have the most need and can be the most impactful is top of mind for companies' manufacturing operations. At MedImmune, the biologics pipeline has expanded quickly from one commercial product to several in a very short timeframe over recent years. Jeong Lee, Principal Scientist at MedImmune continued, "Our priority has been increasing the production throughput either within the existing facility, or converting the existing facility into a multi-product facility where the manufacturing capacity for each product takes up less of a footprint."

At Gilead, Kluck says the priority lies in shortening the process. "Anything that we can do to shorten the product changeove, or shorten our downstream processing times, incorporate more multi-product facility capabilities, this is where we're looking at every step in the process to intensify. If there is a technology or the ability to leverage the harvest depth filtration not just for mechanical separation, but for impurity clearance, that could potentially reduce the impurity clearance burden on the downstream process and shorten our process."

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Another key point is prioritizing technologies that deliver a step change in terms of advancement. Fong said, "The ease of scale is a priority for Genetech because I think we're reaching a point where we see processes advancing a lot faster than technologies. It's important for us to prioritize technologies that we can foresee going beyond what the process challenges are today to what they will be like in 5 or 10 years."

From the supplier perspective, 3M is looking into the harvest space as an opportunity to develop technologies that are purpose made for the industry, given current solutions are borrowed from other applications and simply not ideal given so many challenges. Voloshin explained, "None of the technologies that are widely used today, neither depth filtration nor centrifugation, was specifically designed for biopharmaceutical manufacturing. In fact, both of these technologies and principles have migrated out of other industries, such as industrial separations and small molecule API separations, simply because that's what was available. So we are investigating what new technologies should look like if they are purpose-fit for this industry."

The rule of thumb for new technologies across scientific industries is to make a process cheaper, easier, faster, and better. Certainly the priorities of harvest unit operations center around technologies that make the process better, but at the company level these other factors come into play. Technology developers must factor in the larger goals and initiatives of biopharmaceutical companies to introduce a truly disruptive solution and enable widespread implementation across various manufacturing setups.

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Conclusion

A variety of challenges and needs are driving the demand for next generation harvest technologies and techniques for mAb production. While harvest and purification unit operations adjust to these new challenges internally, there is a need and opportunity for technology developers to hear these unmet needs and create solutions.

New products must deliver on the various unmet needs of the industry that would enable implementation. At the most basic level, new technologies must make a step change in advancement to be implemented given the investment and challenges associated with adopting new technology and changing processes. In terms of the products themselves, demand exists for technologies that are single-use/disposable, universal across various drug platforms, scalable from pilot to commercial scale, predictable as production scales up, do not sacrifice yield, can accommodate expectations for future trends in mAb production, and achieve predictable reproducibility.

Ultimately, as is the case with any changes in biopharmaceutical manufacturing processes, eventual cost savings and a solid ROI must be significant enough for unit operations to justify implementation.

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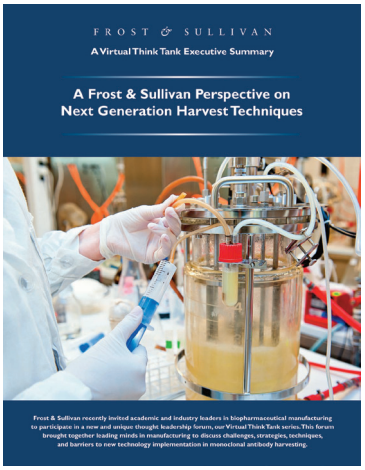

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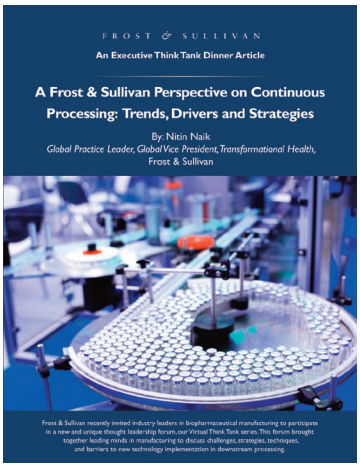

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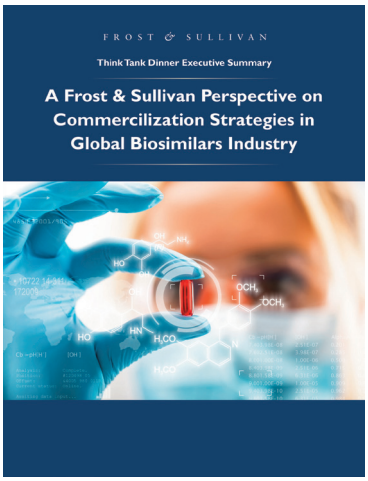

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