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A Virtual Think Tank Executive Summary

Enabling Novel Bioprocessing Technologies Using the Interface of Materials Science Biotechnology

By: Barbara Gilmore, *Senior Consultant, Transformational Health*, Frost & Sullivan

Frost & Sullivan recently invited 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 downstream processing.

MODERERATOR

- **Barbara Gilmore**
  Senior Consultant
  Transformational Health: Life Sciences
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PANELISTS

- **Israel Lidsky**
  Process Scientist
  Regeneron
- **Alexei Voloshin**
  Global Application Strategy Leader
  3M
- **Emre Burak Erkal**
  Upstream and Downstream Process Engineer
  Turgut Pharmaceuticals
- **Geoff Weiss**
  Senior Process Development Engineer
  Sangamo Therapeutics
- **Jim Stout**
  Director Process Science Biologics
  Biovectra
- **Hendri Tjandra**
  Senior Staff Scientist
  Bayer Healthcare

Introduction

Frost & Sullivan recently invited academic and industry leaders in immuno-oncology to participate in a new and unique thought leadership forum, our Virtual Think Tank series. This forum brought together leading minds in this emerging field to discuss next generation bioprocess, implications of research and development occurring today, key challenges, and future approaches to the use of technologies that deliver high productivity, increased manufacturing flexibility and increased speed with reduced risk. The key opinion leaders (KOLs) that contributed to the discussion included:

- Dr. Israel Lidsky, Process Scientist, Regeneron Pharmaceuticals Incorporated
- Dr. Alexei Voloshin, Global Application Strategy Leader, 3M
- Dr. Jim Stout, Director of Process Science Biologics, BioVectra
- Henri Tjandra, Senior Staff Scientist, Bayer US LLC
- Dr. Emre Burak Erkal, Upstream and Downstream Process Engineer, Turgut Pharmaceuticals
- Geoff Weis, Senior Process Engineer, Sangamo Therapeutics

The adoption of next generation bioprocessing is challenged as biopharmaceutical companies grapple with the adoption of new manufacturing methods, which some consider to be essential to the industry's continued growth and innovation. Within the next five years, it is estimated that approximately 35 percent of today's biologics will be manufactured using some sort of process intensification methods. Facilities will be smaller but capable of producing higher volumes of multiple molecules.

The key to this advancement will be the use of methods such as continuous bioprocessing technologies, some of which may be single use, which would enable facilities to reduce both their size and cycle times. The complexity of the bioprocessing industry has challenged companies' innovation efforts, due to potential costs required for changes to take place.

Increasingly complex supply challenges such as the availability of uninterrupted supplies, costs and regulatory scrutiny, play a major role in how companies adapt and innovate. Having multiple staff located in different facilities, in different geographic regions, have challenged some companies, whereas others have working systems in place and hesitate on changing them for newer systems requiring additional regulatory approvals.

Additionally, the challenges involved with the diversification of product pipelines to include cell, gene and RNA therapies, which are making noteworthy advancements, has posed many bioprocessing and supply chain logistics hurdles including managing costs, efficiently moving products while maintaining quality, managing risk and at the same time reducing both capital and operational costs.

Novel Bioprocessing Technologies

The experts who joined Frost & Sullivan's Virtual Think Tank on bioprocessing technologies are studying these developments. While the bioprocessing field continues to evolve, challenges exist in the resource-intensive and highly specialized methods.

Dr. Israel Lidsky, Ph.D., works in the Process Science IPS Management division at Regeneron Pharmaceuticals, in the Process Science Life Cycle Management section. Specifically, he works on crisis control, updating process controls

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> *Global Application Strategy Leader*
> 3M

from elevation activities, and regulatory responses or updates from premature range elevations.

Dr. Alexei Voloshin works at 3M as a Global Application Strategy Leader in the Separation and Purification Sciences Division. 3M is a technology supplier to the biopharma industry primarily in the purification space. Dr. Voloshin focuses on global application strategy for 3M's biopharmaceutical technologies products.

Dr. Jim Stout, Director of Process Science Biologics at BioVectra Incorporated, leads the expansion of a new business entity, working on end-to end solutions. He is currently leading efforts in the microbial therapeutics biologics area to bring genes into the organization, adapting them into a cell line and creating a process to scale up the technology and manufacturing.

Dr. Emre Burak Erkal works as an Upstream and Downstream Process Engineer at Turgut Pharmaceuticals in Istanbul, Turkey, where he specializes in both upstream and downstream process development and scale-up of biosimilar monoclonal antibodies from cell culture. Turgut Pharmaceuticals is Turkey's first biotechnology R&D center established in the field of recombinant monoclonal antibody technology. The center is equipped with state-of the-art bio-manufacturing facilities and is mainly focused on the development of monoclonal biosimilars. Turgut's GMP biotechnology manufacturing facility was designed in collaboration with Merck scientists in compliance with EMM criteria.

Geoff Weiss, Senior Process Development Engineer with Sangamo Therapeutics leads downstream process development efforts for the AAV vector that is used in gene therapies. Sangamo Therapeutics' has clinical trials underway for the treatment of hemophilia, beta thalassemia, inherited metabolic disorders and other difficult to treat diseases with genomic level challenges.

Dr. Hendri Tjandra is a Senior Staff Scientist in the Process Development Division at Bayer. Tjandra leads a group of scientists working on downstream processing of monoclonal antibody therapeutics. He is skilled at the transfer

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> Sangamo Therapeutics

of bench science purification process from both internal and external partners to Bayer scale purification processes.

Next Generation Bioprocessing

Immense progress has been made in the past several years in development of next generation bioprocessing techniques. There are many challenges to overcome before adoption becomes more mainstream, such as the complexity of systems that must comply with numerous regulatory guidelines, some of which are yet to even be defined. In addition, there are gaps in the availability of scientists with the expertise to implement these systems. Finally, the costs of implementation are not insignificant, which is especially important to companies with operating legacy systems already in place.

Adapting Technology or Building From The Ground Up

Biomanufacturing is different from other industries since pharmaceutical and biotechnology companies must comply with extremely stringent regulatory requirements. Changing processes comes not only with the cost of the new technology, but also with the time requirements for obtaining the proper regulatory clearances.

Opinions within the bioprocessing space differ depending upon the perspective of who is asked. Dr. Lidsky noted that "The people on the floor constantly seek innovation, where the people in Regulatory Affairs jobs who oversee and are responsible for the CMC regulations would rather see existing technologies continue to be used." When new technologies are implemented, all regulatory documents must be updated. Dr. Voloshin

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> *Global Application Strategy Leader*
> 3M

echoed Dr. Lidsky, stating, "New technologies can be very sustainable, however when the technology is already accepted by the industry and regulatory bodies, there are less challenges." Geoff Weiss further remarked "If you have existing platforms or processes that work, and you don't have an urgent reason to need to make the change, then don't. If, however, you are creating a new platform or using new products, then using the newest technologies makes ultimate sense."

Though there are more risks with newer platforms, there is less innovation using existing processes. There are always opportunities to replace existing technology with newer platforms, which is a way to keep up with global trends. Changing bioprocessing methods does take time due to the need for regulatory affairs CMC procedures, but in the end usually does lead to better and more efficient processes.

New platforms bring disruptive technologies and breakthrough technologies, especially the fully flexible and disposable platform. Jim Stout remarked that "A full, flexible and disposable platform for the right-sized processing batch and high productivity is the way of the future. Anything that is going to allow very high productivity and very small manufacturing changes to meet clinical requirements is where I see the breakthrough technologies. It is the future of manufacturing to not only right-size and meet the needs of the market to downsize. There is always the need to reduce costs."

From a supplier perspective, Dr. Erkal remarked that "There are expectations for performance. If the new platform is built, there is an expectation of an increase in performance. If the expectation is only 20-50%, then it is best just to keep optimizing the existing platform. If there are other challenges that exist in parallel, such as regulatory hurdles, there is no point to change. If the expectation is 10X higher performance, then obviously it makes ultimate sense to go to the more novel solution."

Barriers To Future Technology

There are barriers to the implementation of new technologies. The bioprocessing industry tends to be fairly conservative. There are reasons to change, and not to change bioprocessing methods. When current technologies are not usable anymore, for whatever reason, it is time to change to more innovative solutions. Geoff Weiss explained, "If something is currently working even though not fully optimized, or the costs are higher than the existing technology, there is a huge barrier to implementing the new technology."

Two barriers to consider when developing an understanding for the rationale related to changing bioprocessing methods are manufacturing scale and type of company. Dr. Lidsky remarked, "The type of company versus how large the research area is will play a role in scaling. If you have a large-scale facility that is dedicated to doing one specific thing, then that company is going to be too invested in that method to want to take on additional risk. If, however you have a large facility that is designed to be modular, that company can grow and divert resources to develop different areas of the facility. Though single-use is a real enabler of that, having the modular compatible facility lets a company bypass some of the barriers to adopt new technologies."

One participant echoed Dr. Lidsky stating, "Some companies are more willing to take on new technologies, but my company sticks with what we have done because the paperwork involved with the use of a new technology is quite tedious, so we make do with what we have in place."

Dr. Erkal elaborated on the regulatory hurdle, stating, "In terms of new technology on the regulatory side of manufacturing, there are definitely significant time periods required to get things approved for use. Implementing new technologies takes time, and there are values for the cost of that time." Geoff Weiss resonated, stating, "It really depends on what changes are planned. Proper risk assessments need to be conducted to be able to carefully weigh the risks versus the rewards." Biomanufacturers are risk averse. Delays in approval have major impacts. The uncertainties around product comparability between scales and process changes are risky. New technologies may not be adopted if there are perceived risks to a program.

Geoff Weiss concluded, "We are completely single use for our entire processes and really is the reason we are doing plain old manufacturing right now. It doesn't make sense for a new company like ours to have anything besides single use."

Finally, there are times where new technologies only work with specific equipment produced by a given company. If you are not a user of that company's equipment to begin with, the capital expense for bioprocess improvements will be formidable.

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> Turgut Pharmaceuticals

Material or Technology Roadblocks Limiting Organizations

In general, both large and small biotech companies as well as CROs, CDMOs and emerging biotech companies are all (to some degree) investing in novel bioprocessing approaches to address different evolving pipelines. The investment may be as small as new buffer management programs to as large as changing manufacturing supply flexibility.

Buffer management, through semi continuous approaches, represents a powerful lever to manage costs and increase facility utilization. Companies typically use bioprocessing paths aligned with their specific molecule pipeline or current manufacturing capabilities. Cost decisions relate to more choice of molecules, volume demands, therapies or biosimilar. Cost pressures drive many of the decisions. By the same token, increasing process productivity is one of the most effective ways to improve facility utilization.

Dr. Erkal remarked "It is the systems and the filters that are important to the whole process on both the development and manufacturing sides that can cause problems. We are always looking for better reasons or benefits to make the whole process more efficient and productive. We are always looking for a better way." Dr. Stout echoed the comments of Dr. Erkal, stating, "There need to be disruptive new materials in downstream processing like getting chromatography to work. We know it is slow and doesn't have the productivity that is needed to move forward for more advanced manufacturing. Advancing membrane chromatography that can in some capacity increase flow rates of membranes would enable this technology. It is still advancing."

Continuous processing or process intensification is something companies are considering. Though well developed in the areas of chemical engineering, biomanufacturing processing leading to smaller and less energy intensive processes are on the radar for many. One participant remarked, "Intensive

processes are something we have to deal with pretty soon. This is going to be a higher and higher priority as the technologies we are expending become less useful. I think companies like 3M have been looking at solving this kind of process problem."

Technologies Being Adopted For Down Stream Processing

Today's processes are often a hybrid of both batch and continuous processes, with upstream processes being less risky than downstream ones. The regulatory concerns related to downstream processes are still developing.

Dr. Erkal remarked "One challenge right now is that we have adopted the use of affinity absorbers as a membrane technology which is a on manufacturing platforms. Some companies are working on this continuous processing technology which will help the whole industry be more productive." One participant concurred, stating, "Continuous processing is a beautiful idea, and a good way to start is continuous capture." Dr. Stout added, "I think there are real opportunities in the future for advancing affinity technologies that work as fast as membrane absorbers work."

Dr. Stout elaborated, "There is a technology from Natrix Separations. We have a proof of concept up to 60 mg/mL at one second resin time. I am familiar with resin times with other technologies, but it still has a way to go."

Driving New Technologies In Downstream Processing

Adoption of new technologies is being driven by bottlenecks according to Dr. Stout. "The manufacturing bottleneck is that the throughput is not adequate. The productivity is not adequate. The impurity reduction is not adequate. These things have led us to do layers of filters, using new materials with higher ligand binding capacity on new resins. We are also using new resins and new multi-mode chromatography."

Dr. Voloshin followed up, stating, "It is the expectation of performance improvement that is driving new technologies in downstream processing. You know the systems you are using, and are either dealing with chemistry or physics or both with ligand chemistries, which affects separation. The performance time, such as the contact time, exerts pressure differential across these systems. It is primarily a function of the physics of the materials themselves. So, as companies want to intensify their process, which means essentially doing more with less, the improvement must focus on both the physics and the chemistry of the type of problem the company is trying to solve separation wise."

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Dr. Lidsky added, "The adoption of new materials would be easier if you already had a molecule that is all in process that is not already validated. To change the production process at that point in time would be very expensive. A company is not going to want to change a process for an already validated molecule. There are however, new molecules coming into a pipeline. They would have the opportunity to do the research with new materials with new molecules in downstream processing and adaptation would likely be a little bit easier." Geoff Weiss concurred, stating, "I would say that some of these changes might be driven by regulatory requirements, so if regulatory agencies change their positions on something, that might drive a change."

Material Science In Downstream Processing

From a material science perspective in the biopharmaceutical space, Dr. Erkal remarked, "The extraction issues are very important. Materials have to be able to be handled easily without any effect on the product." Dr. Stout followed up, stating, "The reproducibility of the material to be able to make it consistently for robustness and control purposes is important."

Dr. Lidsky added, "Along with robustness and consistency, the industry is trying to push biologics to extremes, with higher and higher concentrations of protein. Materials have to be able to handle that consistently. Products need to be monitored throughout, and developed in the first place, to be consistent between lab scale and clinical scale, and not just be developed in large scale."

One participant agreed, stating, "Ease of use and simplicity of the design will be important. I keep this in mind when I develop a product."

Pace Of Technology Introductions

From a Contract and Development Manufacturing Organization (CDMO) perspective, Dr. Stout stated, "Working with other companies and their processes is slow. The pace is slow. There are a lot of regulatory driven changes. What the regulatory space knows is? downstream processing and operations, for molecules have already been through certain types of materials and the regulatory agency has accepted those. Often times though, that is a barrier for new companies or existing companies adopting new technologies. Companies do not want to be first to file."

Dr. Erkel agreed, stating, "From the manufacturer's perspective, it is the development stage where we like to test new technologies to assess their quality and productivity. I agree with Dr. Stout. When it comes to the manufacturing side, the use of new technologies is small. The regulatory just accepts what they know, but when it comes to new technologies, the regulatory side has to be validated."

One participant explained, "It would be great if vendors helped deal with the regulatory issues of getting things validated so they could be done faster and easier. If the vendor has a well characterized package, like a drug master file (DMS) or manufacturing file to it, and approached the regulatory agency or acknowledged a relationship with a regulatory authority, the tech material and everything that has been characterized with it might help facilitate a faster validation for a manufacturer."

Geoff Weiss added, "It is a little bit like the chicken and the egg. It is good to have fully supported products, but until the vendor knows there are going to be sales behind the process, it is hard for them to put all those resources together. It is a market driven activity. There are a lot of vendors who approach us to try things. We have limited bandwidth, so we have to pick and choose what we evaluate. There are a lot of new products and technologies and no shortage of sales reps interested in pushing products." One participant followed up, stating, "Different vendors have different quality controls, so they might think something is well tested but they had pushed an earlier version to us and validated a later one."

Dr. Lidsky added, "One technology I don't see much of is management software tracking different products going through the process. There are electronic batch sheets that have their own software package. What about software for managing end-to-end besides tracking the batch numbers? There can be more of a dynamic response if you detect something so you will be able to respond to it more swiftly."

Geoff Weiss gave his input by stating, "We are looking at the same thing. We are evaluating a company called Riffin in the San Francisco Bay Area that came

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out of another company called Codexis. These guys developed an in-house system called Crosstalk that incorporates all the processes you can input either online or manually to track individual processes. It is a global system that can see what is happening in general in your system."

"Our panelists cautioned that there is no "end-to-end solution," but there are technologies in development to innovate the existing downstream processes."

Conclusion

There are hurdles and challenges to the adoption of novel bioprocessing technologies in the biomanufacturing space for all companies playing in the biomanufacturing space, from established biotech, emerging biotech's to CDMOs. The most common concern for all involved is the regulatory hurdles that must be overcome to adopt new technologies in downstream processes. Strategies targeted to areas where bottlenecks occur, coupled with better membrane extraction to software tracking end-to-end processes that come with vendor associated MSDs or regulatory master files would facilitate faster adoption.

Our panelists cautioned that there is no "end-to-end solution," but there are technologies in development to innovate the existing downstream processes. Costs and regulatory validation topped the list of drivers to facilitate greater implementation. The use of strategic partners and vendors who are knowledgeable about the hurdles and barriers to successfully implement next-generation bioprocessing would facilitate greater adoption rates. To remain competitive, early adopter biomanufacturers would benefit from collaborations with both vendors and regulators to most efficiently use new processes. Improving both product quality, while reducing process and product variability and increasing the quality of the yields will increase the company's bottom line. Companies would rather be a fast second than a slow first when it comes to adoption of a new innovative technology.

Frost & Sullivan would like to thank the thought leaders who joined our Virtual Think Tank for their time and valuable insights into this promising field. We hope that this discussion spurs new ideas and fosters additional exchanges for this burgeoning area.

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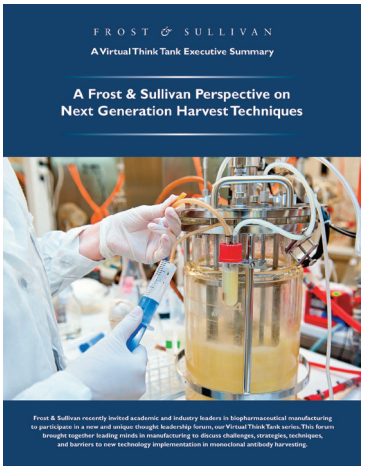
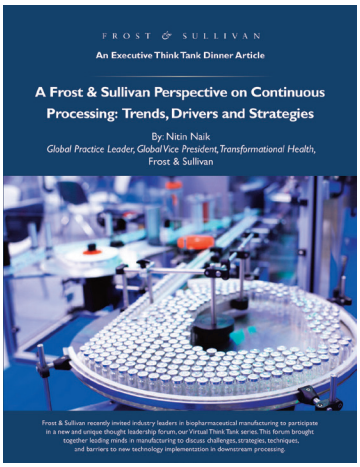
Key Trends Reshaping The Future of Bio-pharmaceutical Harvest and Clarification



Perspective on Next Generation Harvest Techniques

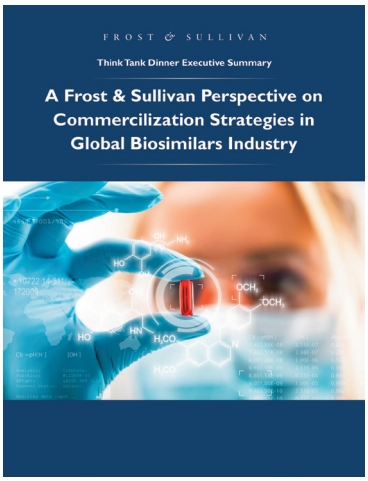
Transition to Next Gen Down-stream Processing to Capitalize on Growth Opportunities in High-Value Low-Volume Biologics

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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