FROST & SULLIVAN

A Virtual Think Tank Executive Summary

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

By: Unmesh Lal, *Program Manager, 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.

Challenges in Downstream Bioprocessing Necessitate Disruptive Purification Strategies

Unmesh Lal opened the discussion by noting that the increasing demand for biologics is driving the need for innovation in bioprocessing. The primary goal of downstream processing is the isolation and purification of the desired protein or nucleotide from the bacterial or animal cells that produce it in a fermentation process.

The fermentation processes that are used by biopharmaceutical manufacturers have shown to lead to increasing quantities of therapeutic proteins. Manufacturers are increasingly recognizing the present need for improvement and have shifted their focus from improving the upstream process to improving the downstream process. Umang Trivedi said, "The problem that we are facing right now is some of the inefficiencies in the process which are being brought to the forefront because of the increased titres, increased cell densities that are coming out of the upstream processes."

Challenges in downstream bioprocessing are driven by the pipeline growth of variable and complex emerging molecules such as bispecific antibodies, monoclonal antibodies (mAbs), antibodydrug conjugates (ADCs), and viral vectors for gene and cell therapies. From a CDMO (Contract Development & Manufacturing Organization) perspective, Paul Jorjorian, stated "this problem of flexibility that you have some molecules that are demanding metric tons, and then you have some that are, maybe it's a couple batches a year." Echoing Paul, Russell Overbeck questions "How do we device

PANELISTS

- **Christopher Gillespie**
  Associate Director, Downstream Process Development
  Immunogen Inc.
- **Paul Jorjorian**
  Head of BioProcess Sciences
  Thermo Fischer
- **Umang Trivedi**
  Associate Director, Global Tech Ops
  Merck & Co.
- **Alexei Voloshin**
  Global Application Strategy Leader
  3M
- **Darshini Shah**
  Senior Scientist Downstream Process Development
  Patheon
- **Andrew Tustain**
  Associate Director
  Regeneron
- **Hiren D. Ardesna**
  Senior Scientific Investigator, Downstream Process Development
  GlaxoSmithKline Inc.
- **Jennifer Pollard**
  Senior Scientific Investigator
  Merck & Co.
- **Russell Overbeck**
  Principal Scientist
  Boehringer Ingelheim

strategies for dealing with molecules where yes, we only need to make two to three batches a year?" He continues to state that there is a need for strategies and technology to be able to at least meet these new challenges in an innovative way – so we're not treating different products the same way. Umang Trivedi contributes to the requirement for flexibility by commenting that that while suppliers like GE, Sartorius, Pall, Millipore continue to make progress in downstream, we need to focus on verification strategies which will allow us to produce large amounts of drug substance using the smallest manufacturing footprints.

From a different perspective, Andrew Tustian notes that it is not that we require completely disruptive purification strategies but a kind of an intensification and industrialization of the existing technologies. Jennifer Pollard supports the opinion stating, "A lot of the challenges that we've been facing is just trying to do developments faster- this whole idea of accelerating to the clinic. We do not necessarily need very disruptive verification strategies because there's not always time to completely revamp something."

KEY TAKEAWAYS:

- New developments in novel biologics and expansion in upstream throughput demands improvements in downstream capabilities.
- While new downstream technologies are emerging to increase throughput times, reduce human resources and process development costs and increase yield, downstream processing is still seen as the main technology bottleneck in the processing of biopharmaceuticals.

"We need to focus on verification strategies which will allow us to produce large amounts of drug substance using the smallest manufacturing footprints."

— Umang Trivedi,
Associate Director, Global Tech Ops
Merck & Co.

Implications of Small Batch Pseudo and Fully Personalized Therapeutic Development

Regenerative medicine and immunotherapy are at the forefront of biomedical research and are used to treat a variety of medical conditions such as cancer, neurodegenerative and other orphan diseases for which most of the currently available treatments are rather palliative.

Investments across complex immunotherapies, alongside a strong potential for personalized cell and gene therapies is shifting the market paradigm towards low-volume high-value biologics manufacturing. In particular, with the recently launched therapies Kymriah and Yescarta, and an increasing number of products reaching late phase clinical trials, there will be a growing need for increased large-scale manufacturing capacity. Manufacturing hurdles include the challenge that many of the T-cell processes involve very personalized patient specific production. This commercialization of gene and cell therapies requires industrialized production approaches, which will drive technology innovation downstream.

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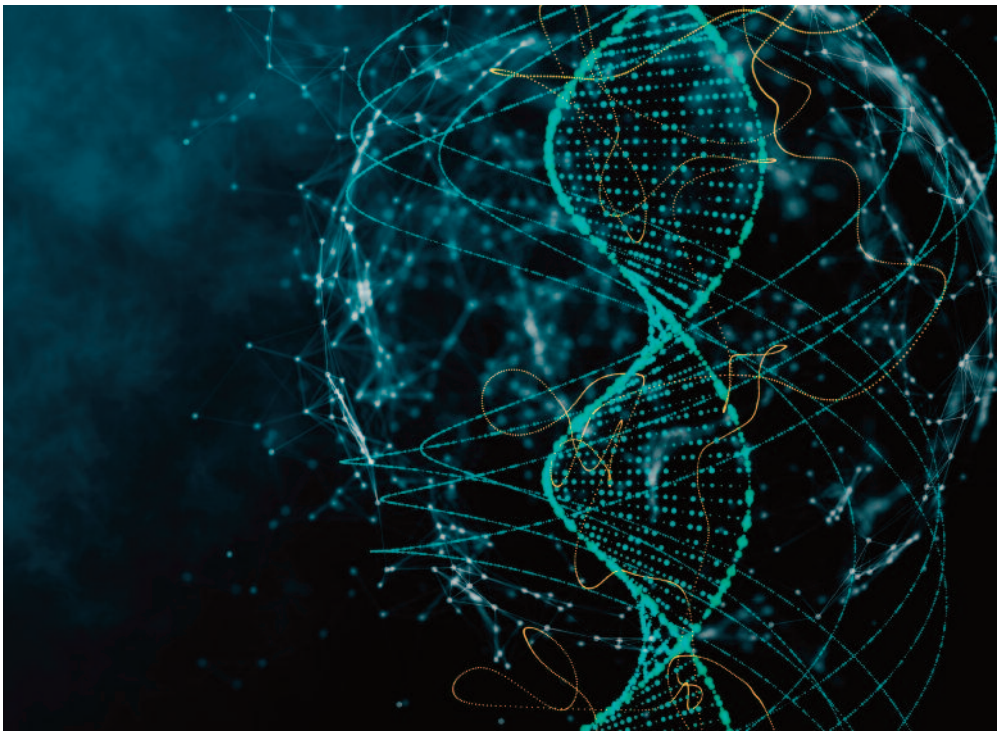
>
> **— Umang Trivedi,**
> *Associate Director, Global Tech Ops*
> Merck & Co.

The key driver of these new modalities is shortening the production process, thereby reducing the time required to get the product to the patient. There is a demand for technologies that companies can adapt to intensify the production process without having to modify their existing manufacturing facility. Umang Trivedi emphasized "Effective characterization is the key, effective characterization of the product and then the process, how we can develop the robust control strategy of these new modalities." Highlighting the requirement for smaller biotechs in regards to their collaborations with CDMOs, Christopher Gillespie commented, " We don't have our own independent manufacturing capabilities and we're using CMOs to partner and do these types of developments. And so having different types of technologies that are accessible across the, I guess CMO networks, would be something very advantageous. However, somebody like us would probably be more risk averse of going towards some of these new technologies."

Adeno-associated virus (AAV) vectors have become one of the best fitted platform technologies for in vivo gene therapy, mainly due to their valuable safety profile and their highly efficient transduction for various target tissues. This requires all downstream purification steps to be upscaled while removing holdups present in traditional biomanufacturing methods. Andrew Tustian explained, " The size may push you towards membranes and monoliths. And also it may push you to more kind of contained, fully contained system, so the kind of disposable systems that you can contain."

Russell Overbeck elaborated "But certainly when you look at cost of goods and things of that nature even from a development standpoint, in order for these strategies to work, I think you're moving towards what would need to be high capacity, inexpensive, single use, disposable purification technology that could potentially be portable." Paul Jorjorian echoed the future of smart factories while providing a different perspective stating "That as you go to fully personalized, It's almost equipment that is close to the patient, I always have envisioned, all of the stuff is going to move into the hospitals or to sort of care centers, akin to sort of dialysis centers if you think about it at some point, just because I think that's the only place where you can even start to think about rolling out on a large scale and achieving the costs that are reasonable for these types of therapies." Jennifer Pollard added "So a small profusion bioreactor attached in a closed system, the columns, and ending up sort of in a filled vial, all within like a bench top unit. That's sort of what that's going to look like. It's not going to be a factory, it's going to be some sort of clinical module."



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"Even if you work with the monoclonal antibodies, or even if you work with the new modalities, are you answering the right question, are you testing the right attributes to release this product into the market to kind of satisfy the safety and efficacy requirement."

— Alexei Voloshin,
Global Application Strategy Leader
3M

Andrew Tustian concluded, "To achieve fully personalized medicine signifies that there is no more separation between your product and your product is your process because you're never going to fully validate your products since you're always making a new product. What you can validate is the fact that your process will produce a product in a certain scaffold family with certain quality and certain efficacy."

KEY TAKEAWAYS:

- Cell and gene therapy is a highly invested area growing at a CAGR of 22.0% between 2017-22.
- With the advent of new modalities, there is an expected shift to flexible, small-volume manufacturing comprising of single-use systems exploring continuous processing technologies in modular facilities.

Rethinking Collaborative Partnerships

As biopharma manufacturing involves challenges from governmental regulations to complex business models, the key pharma players in the market are increasingly focusing on collaborating with players including biotech, CDMOs, CROs as well as regulators and technology vendors to meet the evolving needs of the industry.

Being a highly regulated environment; timelines for the development and adoption of new technologies are lengthy. Concerns were raised, "Even if you work with the monoclonal antibodies, or even if you work with the new modalities, are you answering the right question, are you testing the right attributes to release this product into the market to kind of satisfy the safety and efficacy requirement." Alexei added, "And so the question is that every single time you improve something, it will be either through a cell line or through a certain purification technology, what are you giving up. And the things that you're giving up in terms of either performance, quality, or robustness, are they making your process riskier, both in terms of the risk to the patient, but also the risk of technical failure of the process itself as it migrates into commercial manufacturing. I think that's an area that should be scrutinized quite heavily as the improvements and disruption in these processes accelerates."

Connected factories and manufacturing error free are the tenets for flexible manufacturing solution providers. Umang Trivedi questioned, "Can't we reduce that human kind of operation to make our process much more robust? Can't we have more automation in our process to gain this productivity and performance? We need to connect all these different IT systems at some point to make it our digitalization much more efficient. So we can have the access of all the right data at the right time." Paul Jorjorian explained, " I think there's also this question about how the data – these technology suppliers especially in the world of single use manufacturing, but certainly applies to things like media, media components etc. flows in to what's occurring within the shop floor." Jennifer Pollard emphasized "We need to have collaborative relationships between the industry and technology suppliers."

Corroborating the need for partnerships with technology suppliers, Alexei Voloshin commented "3M as a material science company, we can actually go look into our toolkit and to be able to understand what it is that we can bring from this toolkit in order to make products which address some of these sort of changing paradigms that we've talked about today, for example such as some of these newer modalities which not only require sort of different chemistries but different physics as well because of their biophysical characteristics."

Panelists agreed that a standard format for connectors, filters and columns, would make the implementation of a new technology easier. As an industry, pharma companies need to communicate with technology suppliers in regards to their challenges and feedback about their products. An additional benefit of these intra-industry collaborations would be to ease the filing burden, and other regulatory hurdles that companies face.

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KEY TAKEAWAYS:

- There is a need for digital continuity, connecting data to manufacturing decisions across the value chain.
- There is a focus to improve productivity and have platformable processes for these new modalities, while meeting the high quality and regulatory standards for the therapeutic.
- Collaboration and partnerships is the key to having the most advanced bioprocessing technologies.

Conclusion

A robust biologics pipeline coupled with a high growth rate is transforming the biopharma manufacturing landscape. As the industry transitions from "small molecule" to "large molecule" manufacturing, advancements in downstream processing is necessary in removing purification bottlenecks, streamlining development, and reducing cost, complexity, and risks associated with biopharmaceutical production. Innovation in functional chemistries and materials science are creating opportunities for technology suppliers in integrating upstream and downstream unit operations, buffer management and handling, highly selective affinity resins, membrane chromatography, depth filtration systems etc.

Owing to this growing demand for biologics and biosimilars with complex manufacturing requirements alongside a capital-intensive market, many pharmaceutical companies are seeing the profitability in collaborating with CDMOs and technology vendors for both clinical and commercial stage manufacturing. Unified strategies will further ease the interaction with the regulatory bodies, ultimately resulting in high quality and timely launches, increased operational excellence and continuous improvement in manufacturing.