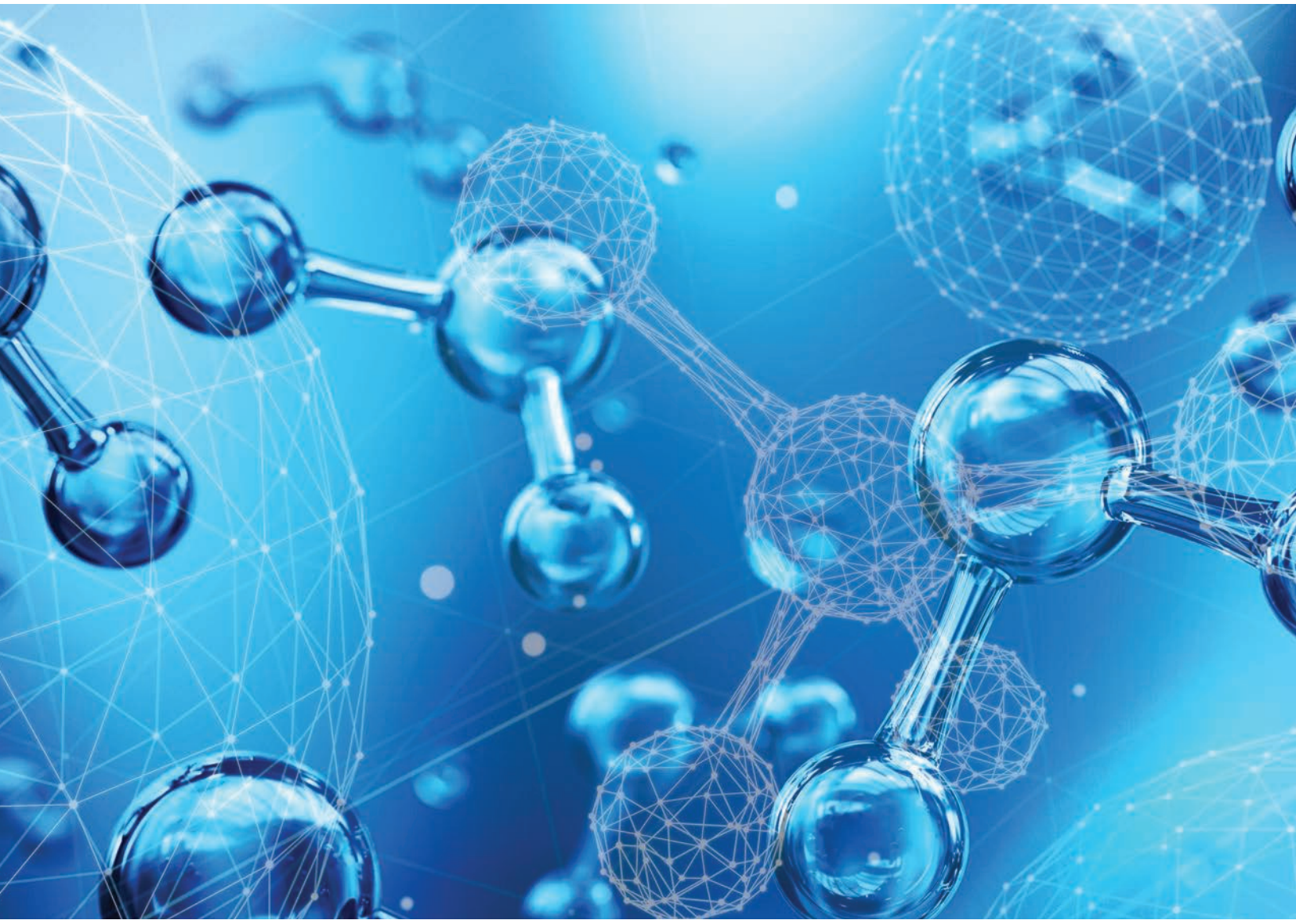

Article: A Frost & Sullivan Webinar Summary

Preparing for Next-Generation (or Future) Biopharmaceutical Manufacturing

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This article was derived from a recent webinar

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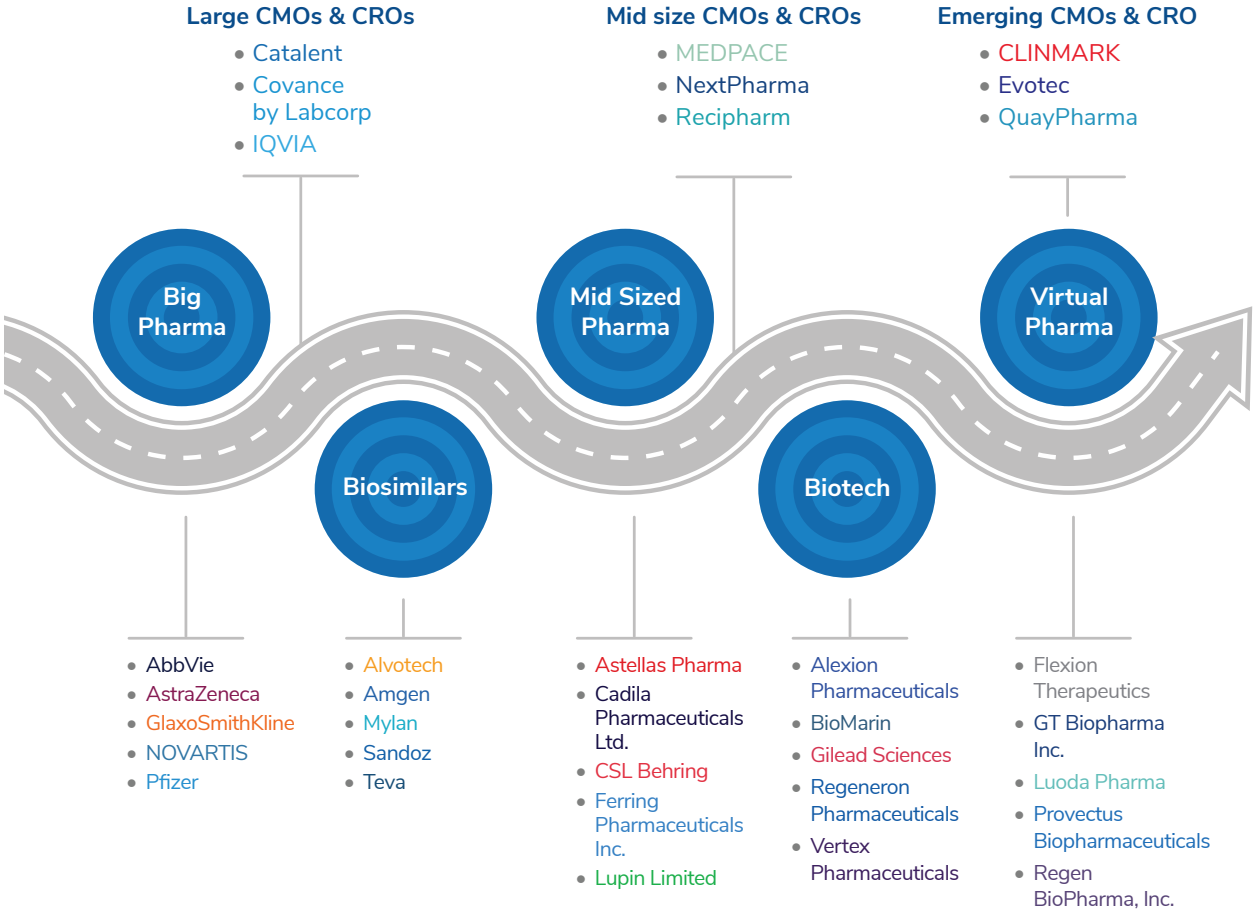
Biopharmaceutical Companies Stake Out Claim to Launch Best-in-Class Assets

Drug pricing challenges, exacerbated by the CoVID-19 pandemic, mounting labor costs and an uncertain economic landscape are all affecting performance of the biopharmaceutical industry. Ongoing pressures to update legacy biopharmaceutical systems and processes and integrate upstream and downstream bioprocessing workflows round out the many obstacles to overcome.

The biopharmaceutical industry, along with the Contract Research Organization (CRO) community, has invested significant research and development dollars to develop a strong clinical pipeline: 992 phase 3 studies for biological molecules (Source: clinicaltrials.gov as of March 2021). Responding to the rapidly changing manufacturing requirements of these novel biologic therapies means tackling some of the biggest challenges that have the potential to hinder this evolution. One such area is productivity improvement and technology advancements in manufacturing. From a manufacturing perspective, stringent requirements to achieve consistent quality are driving companies to optimize their operations. This requires a holistic approach to re-engineer manufacturing, both at the front end and at the downstream commercial stages.

Figure 1: Bets on Novel Targets and Next-Generation Manufacturing Drive External Partnerships



CMO= Contract Manufacturing Organisation; CRO= Contract Research Organisation; CDMO

Source: Frost & Sullivan, Company Websites

Pharmabio, CDMOs Nail Down Solid Investments, Unlocking Door to Wave of New Opportunities

Genentech's Investment Pilot Plant, a manufacturing test facility where scientists and engineers determine the best way to make medicines at larger scale, is a great example of a biopharmaceutical company pushing the boundaries of technical innovation and process optimization. While monoclonal antibodies have been going strong for the last decade, several new products such as CAR-T cell therapies are also injecting energy into the field.

Several biotech companies are pushing new biologic candidates in the clinic. This will increase demand for bioprocessing and also bring new technical challenges. These challenges will mandate partnerships with leading contract development and manufacturing organizations (CDMOs) to accelerate development. Catalent, a global CDMO with proprietary platforms for cell line development, has been working with multiple generation platforms from a quality and a development standpoint.

Frost & Sullivan has identified six dynamic trends that will impact the future of biopharmaceutical manufacturing:

1. **Embracing Technology Advances**: Pharmaceutical and biotech companies need to invest and embrace technology platform advances such as antibody-drug conjugates, combination therapies, next-generation CAR-Ts and emerging RNA and immunomodulation therapies.

2. **Next-Generation Manufacturing Methods**: While continuous process is being increasingly adopted, companies should evaluate factors such as production capacity, product demand and number of products on the portfolio before deciding to adopt continuous or single-use technology especially for manufacturing of monoclonal antibodies (mAbs).

3. **Cost Optimization for Clinical Development**: The increasing R&D expenditure year-on-year and the probable impact of CoVID-19 on the R&D budgets of companies will necessitate the adoption of smart tools such as virtual clinical trials, which can not only reduce per patient trial costs, but also offer enhanced efficiency and patient compliance.

4. **Advances in Recombinant DNA Technologies**: This has facilitated large-scale manufacturing of biologics products such as human growth factors, mAbs and fusion proteins. In addition, improvements in analytical technologies have enabled improved characterization of macromolecules, including proteins and nucleic acids, which allow for the screening and identification of novel biologics with complex structures and various therapeutic functions.

5. **Single-use Technologies**: These platforms increase flexibility and improve closed systems, resulting in decreased capital cost and decreased total cost of goods sold (COGS) over the lifetime of a product.

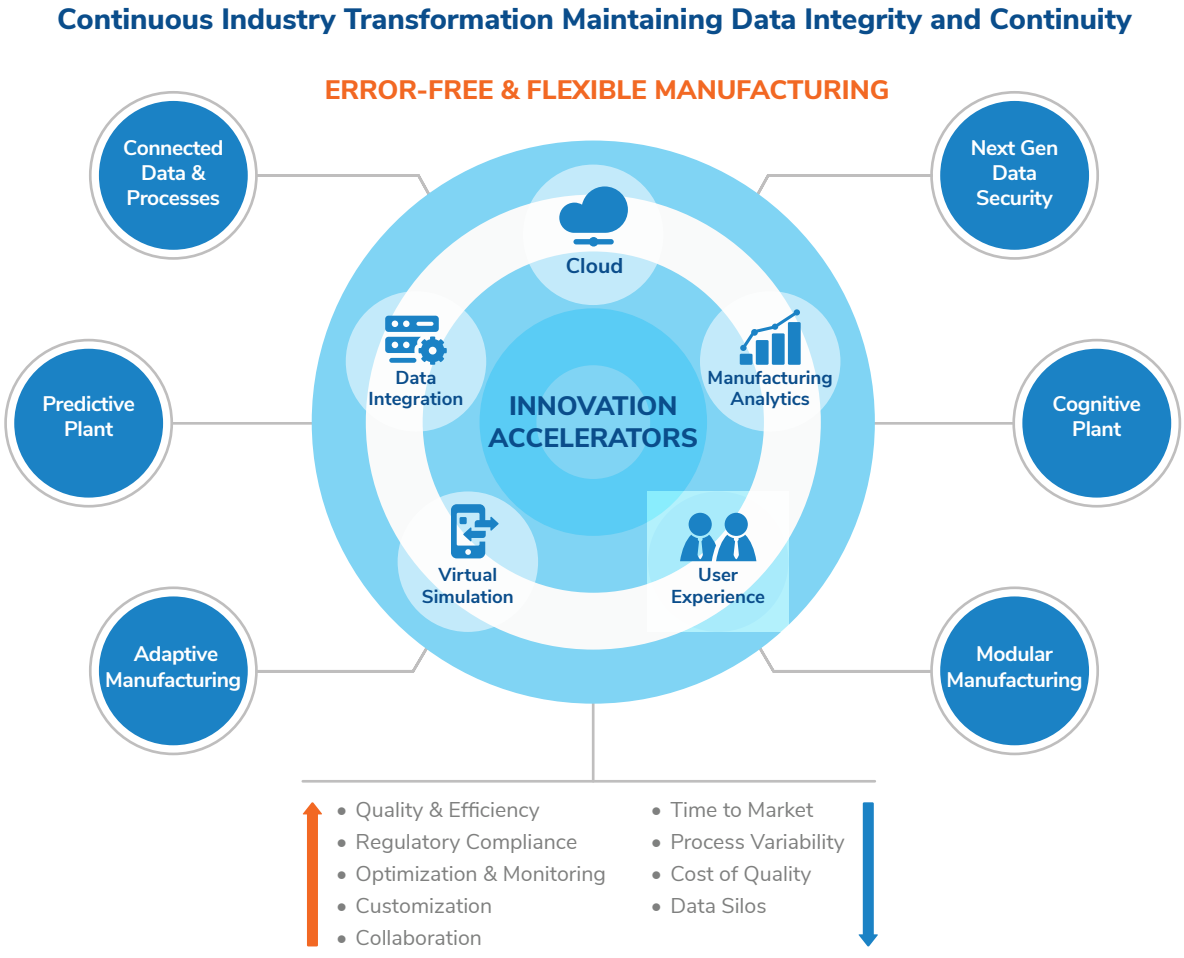
6. **Process Analytics**: The emergence of smaller and faster analyzers have helped companies increasingly adopt process analytical technology (PAT), and this is a trend that is likely to continue in the future. PAT is likely to improve the quality of bio-monitoring programs while also enabling greater production and cost savings. By enabling better process understanding and process control, PAT will lead to superior process optimization, cost savings and drive adoption of continuous processing.

Win or Lose in Precision Health, Biopharmaceutical Manufacturing Takes Shot at Error-Free and Flexible Manufacturing

Despite rapid growth in clinical development and manufacturing data volumes, siloed approaches within biopharmaceutical companies have challenged their ability to arrive at something that is more powerful to drive decision-making. While companies have good experience in optimizing manufacturing workflows, partnering with bioprocessing suppliers will help them find new and better ways to harness the power of flexible manufacturing.

Rick St. John, Head of Digital Sciences, Genentech, Inc., pointed out that it is important for biopharmaceutical companies to strategize development of data-driven technologies to manage not only large volume products, but also in a cost effective way, to be able to manufacture even the smallest batch for an individual patient (Figure 2).

Figure 2: Data-Driven Biopharmaceutical Manufacturing Making Precision Health a Reality



Source: Frost & Sullivan

He further suggested that, for personalized therapies, the numbers of batches (per patient) increase by four to five orders of magnitude versus traditional manufacturing operations. This is a big change that demands exponential improvements; otherwise, the cost is going to be prohibitive and not scalable. The next step for the biopharmaceutical industry is to integrate existing mature technologies with more advanced digital technologies to move into Error-Free and Flexible Manufacturing. By 2030, Error-Free manufacturing will emerge as a de facto standard. This is especially important for personalized therapies that are critical for late-stage patients who may not survive if a batch fails. This is a really important topic for partnerships between bio purification suppliers and biopharmaceutical companies to have an end-to-end solution view for the industry.

> **The next step for the biopharmaceutical industry is to integrate existing mature technologies with more advanced digital technologies to move into Error-Free and Flexible Manufacturing.**

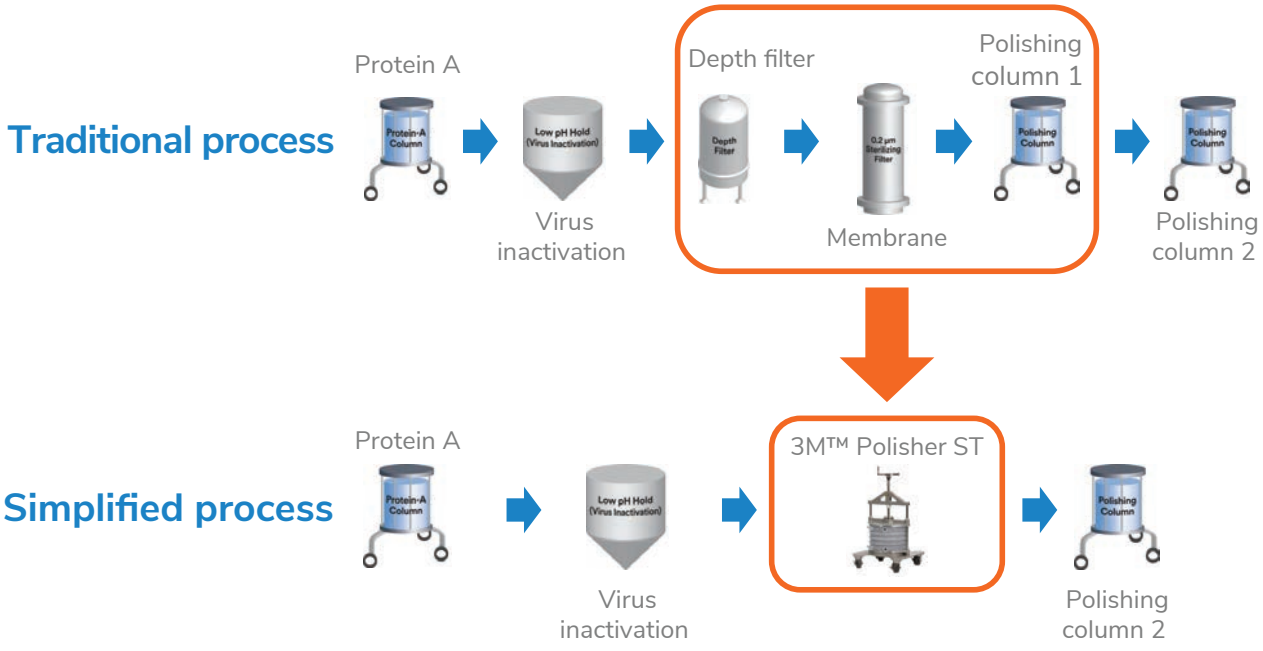
3M™ Polisher ST Replacing Chromatography Column at Scale

Biopharmaceutical companies are approaching the limits of manufacturing productivity and scalability, and innovative downstream bioprocessing (DSP) solutions are required to address these challenging issues. The bottleneck in process-scale chromatography negates any advantages of scaling up earlier process units because bind-and-elute chromatography steps are driven by product mass rather than volume.

This means that savings made upstream do not translate into increased productivity during purification. Larger columns also impact facility layouts, costs and infrastructure because space and buffer volumes for all steps also increase. As a consequence, pool and buffer volumes act as serious limitations when it comes to the introduction of high-titer processes into existing facilities.

Matt Peters, Application Development Specialist, 3M, pointed out that these trends are accelerating the transition to single use membrane chromatography (Figure 3).

Figure 3: Simplification of the Polishing Train



Source: Frost & Sullivan

He further explained how 3M™ Polisher ST enables this transition through a novel guanidinium based chemistry and advanced material science. 3M™ Polisher ST offers not only economic benefits and versatility, but it also has specific functional advantages over equivalent packed-bed columns. These are:

- **Convenience**—There is no cleaning validation, no packing, re-packing and recycling.
- **Scalability**—A production scale capsule of 1.6 m² can replace a packed column of 80 liters. Capsules can be stacked for even higher loadings.
- **Small Footprint**—Use of one-fifth (20%) of the buffer volume compared to a column of equal capacity, saving time and money. Lower buffer volumes in the purification process drive down wastewater that needs to be handled for disposal.

PERSPECTIVES FROM PANEL:
Future of mAb Manufacturing Platforms and Emerging Process Technologies for Modalities (Gene to Protein)

St. John articulated the need to innovate and create manufacturing strategies that are as standardized as possible for the future.

Steven Hager, Director, Science and Technology, Catalent Biologics, stated, “One of the huge drivers for antibody development is to have better control over processes, as well as minimizing human interaction, to reduce deviations and to create a product that's safe and reliable for patients.”

George Buchman, Vice President, Preclinical and Process Development, Catalent Cell and Gene Therapy, stated, “We definitely appreciate the lessons learned from mAb technology development over the past several decades, from single use technologies to stable cell lines and new filtration technologies.”

Alexei Voloshin, Global Manager of Biopharma Application Development, 3M, stated, “It is important to review both physical and chemical characteristics of biologics and to create systems that are innately geared and designed to be able to affect both expression and purification of the systems.”

PERSPECTIVES FROM PANEL:
Designing New Process Platforms (Based On Learnings from mAb Manufacturing) and Digital Technologies to Transform In Clinical Development and Manufacturing

Hager emphasized the need to match the cell and gene therapy processes to the scale. He explained the need to rapidly develop digital controls for analysis and detection of process drifts to minimize issues and ensure consistency.

Discussing digital technologies, St. John stated, “For antibodies, we're really in a phase of industrialization. So, we're thinking about efficiency, maturing to a point of review by exception, automated release, and transitioning to highly reproducible and on-demand consistent manufacturing. So, digital technologies are super important in terms of monitoring, control and interconnectivity between unit operations in a manufacturing process.”

Buchman recommended opportunities that take advantage of viral vector chemical characteristics to eliminate process-related impurities and leverage evolving technologies to make progress. As he summed up, “Getting staff to use these tools is also a focus area for lots of us in the industry.”

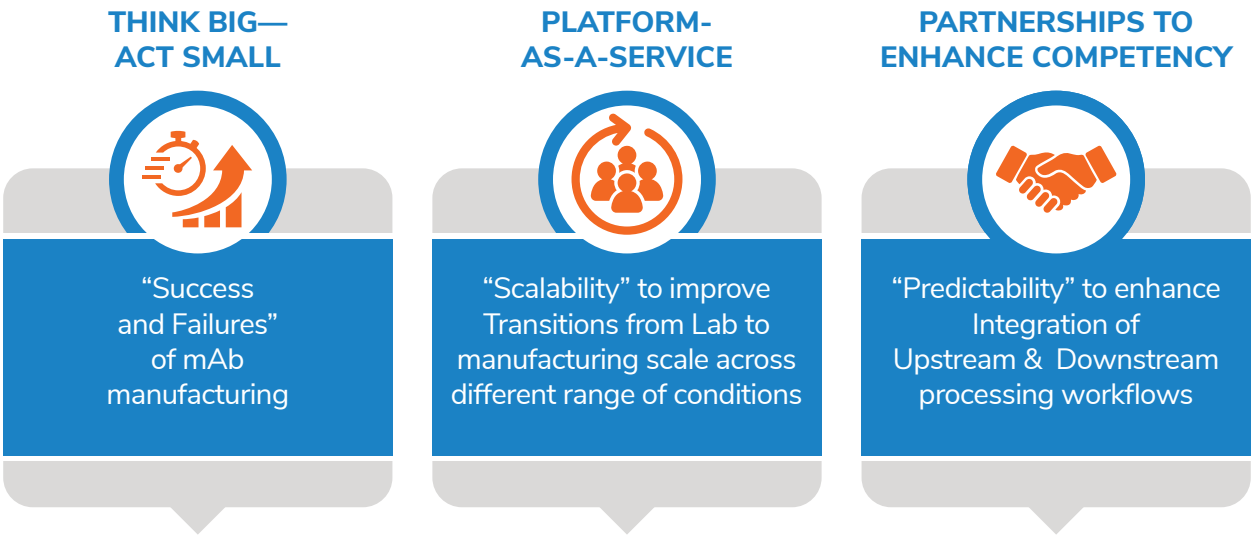
Voloshin noted that when he thinks about digital technologies, he thinks about the importance of data acquisition and possibilities for them to become predictive. He further stated, “You can build a lot of these processes ranging from production to separation of these entities, predictably, in silico. As we build more advanced technologies, which are mainly simpler, their interactions are more defined, and they are made a lot more precisely, which means that batch-to-batch variation is lower. These are very exciting capabilities.”

'Missing Link': Digital Technologies Help Biopharmaceutical Industry Catapult to Next-Generation Platforms

While the early days for mAbs were a bit unsteady, the science behind these therapies is now well accepted. While comparing developments in the cell and gene therapies to what industry has seen in the mAb space, there are many important lessons that can push the current results coming from the clinic for cell and gene therapies.

Nitin Naik, Global Practice Area Leader, Healthcare & Life Sciences, Frost & Sullivan, noted, “We strongly believe innovative digital technologies will be required to address challenges faced by biopharmaceutical companies to overcome limits on manufacturing productivity and scalability. We clearly see that access to data is just not enough. The industry needs different bioprocessing use cases, and they will be a key differentiator either around real-time analytics or factory-in-a-box solution. There are three considerations that are important to continue this momentum." (Figure 4).

Figure 4: Partnerships between Pharmabio, CDMOs, Bioprocessing Suppliers will become indispensable



Source: Frost & Sullivan

He concluded, “Learnings from the success and failures of the mAb are critical to set the stage for platform ability. Then, once that broader infrastructure and architecture is in place, biopharmaceutical companies should address the different transitions moving from lab to manufacturing scale across different range of conditions. That's where the scalability becomes an important part of the conversation. Finally, predictability will be an important component, looking at integration of upstream processing and downstream processing workflows.”

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