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An Executive Think Tank Dinner Article

Cell Therapy Biomanufacturing: Trends and Perspectives

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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.

PANELISTS

- **Brian Hawkins, Ph.D**
  Scientific Applications Director
  BioLife Solutions
- **EJ Brandreth**
  Vice President Global Quality
  Inovio
- **Michael Blackton**
  Vice President, Quality Assurance and CMC
  Adaptimmune LLC
- **Heidi Hagen**
  Chief Strategy Officer
  Vineti
- **David Smith**
  Head of Innovation and Engineering
  Therapeutics Solutions
- **David Weiner, Ph.D**
  Executive Vice President
  The Wistar Institute
- **Ohad Karnieli, Ph.D**
  CEO & Co-Founder
  ATVIO Biotech Ltd.
- **Thomas Page, Ph. D**
  Development
  FujiFilm Diosynth
- **Alireza Abazari, Ph. D**
  Scientific Applications Director
  BioLife Solutions

Overall Perspective

Present unmet needs and remaining challenges

Cell therapies constitute one of the most prosperous fields of research, as they advanceing the creation of new companies offering both products and services within a vast range of logical innovations, from autologous cell transplantation in the clinics to cell-printed tissue for research use and validation tests in pharmaceutical development. According to Frost & Sullivan, the cell therapy manufacturing industry is expected to experience a great revolution in terms of products launched and customer niches penetrated in the next five years. Therefore, costs associated with cycle developmental time around novel solutions become decisive for commercialization success. Flexible manufacturing platforms and smart-based quality control systems embracing a broad spectrum of adjacent technology solutions are poised to lead the way toward world-class, high performance, cost-effective cell therapy manufacturing platforms and facilities.

Biomanufacturing strategies for cell-based therapies diverge significantly from conventional models best suited for non-cellular pharmaceuticals and traditional biologics. Rivière and Roy, 2017, emphasize the unique commercialization challenges in terms of manufacturing, standardization, and distribution that cell therapies face being living drugs. Therefore, a crucial demand for more flexible platforms capable of addressing the challenge of manufacturing cell-based products at large scale and dealing with both allogeneic and autologous biotherapeutics has been evidenced, especially during the past two years. Ideally, cell therapy manufacturing platforms should be able to scale up and scalei out without losing control over the cell culture environment and bioprocess stages.

Scaling of production processes is the highest cited challenge, followed by development of next-gen characterization techniques and access to fully automated closed-loop systems that ensure sterility. On scaling, it is clear that personalization of therapy is driving down production volumes and pilot scale stirred reactors of 50L are near the top end of the spectrum with much smaller capacity reactors of 2L to 10L being standard-issue at most production facilities for next gen therapeutics. The larger sized reactors are more an outlier, restricted for specific application areas like platelet production.

David Smith added to the conversation by stating "The production process is challenging, each step has nuances, like the idea of getting smaller and smaller and personalized production for cells."

Another key concern in scaling is the standardization of raw materials as shared by John Rowley, COO of Rooster Bio "Strategically, the standardization of raw materials into processing is the challenge, but we still need to get production vessels, single use disposals from suppliers." Development & deployment of single use systems and technologies is another key área of growing need in the área of cell therapy commercialization.

In addition to automated, robust, and cost-effective production platforms compliant with current good manufacturing practices (cGMP), opportunities for improvement comprise: 1) raw material characterization and control; 2) smart sensors for advanced in-line monitoring systems; 3) artificial intelligence learning methods for multivariate analysis, predictive models and closed-feedback control loops; 4) technological advancements in rapid analytical testing for biological assays; 5) integrated and streamlined quality and business systems to enable flexibility; and 6) cohesive regulatory strategies. Figure 2 illustrates key approaches optimizing biomanufacturing with more agile and cost-affordable solutions.

As batch numbers increase, complex logistical challenges also increase concomitantly, like scaling out production to multiple manufacturing sites or in proximity to the patient within hospital settings. This is further compounded by the regulatory requirements to maintain comparability between sites. As batch numbers increase, chain of custody becomes an issue, and it is important to track end to end the origin and final end-point for each dose. Karen Albertson of 3M noted "With fourteen thousand doses a year, chain of custody can be an issue."

PANELISTS

- **Richard Stout**
  Director of Global Sourcing and Procurement
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- **Jon Rowley**
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- **Gregory Block**
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- **Wen Bo Wang**
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- **Vered Caplan**
  Chief Executive Officer
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- **Karen Albertson**
  Global Business Director
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  Global Product Marketing Manager
  3M
- **Kristin Jacobsen**
  Marketing Development Supervisor
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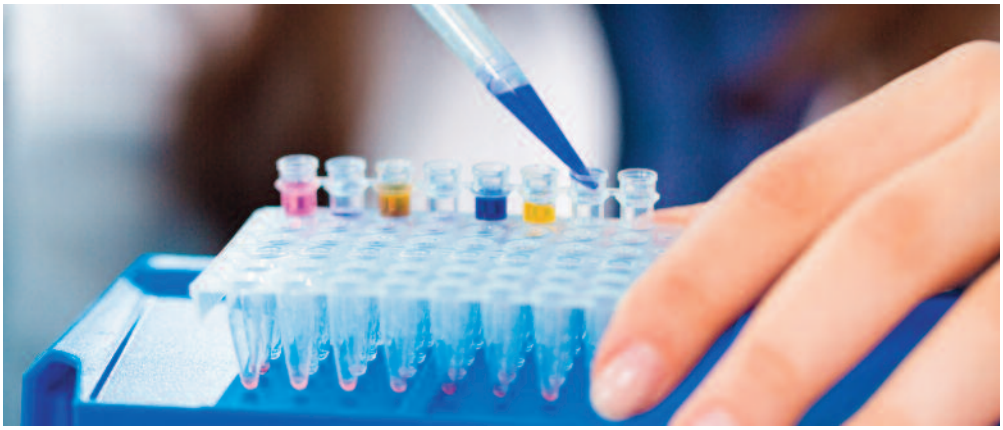
Beyond chain of custody, batch disposition constitutes a key bottleneck in biomanufacturing. Analytical tests at the end of the production batch involve long lead-time, human-operated, paper-driven systems. The successful implementation of real time releasing solutions encourages biomanufacturers to consider the special attributes of their industry, particularly sterility and the measurement of viral and microbial contamination, as well as, microbial contamination through instruments. Technology convergence toward novel in-line sensor technologies is key for the biomanufacturing sector to leverage the potential of real time releasing biomonitoring. This was underscored in our survey results with several respondents indicating the access to fully automated closed-loop systems ensuring sterility was a key challenge or requirement. Eventually, testing may give way to environmental monitoring with the integration of more automation and perhaps be influenced by the evolution of the regulatory thought process, eventually transforming the entire process.

> "Strategically, the standardization of raw materials into processing is the challenge, but we still need to get production vessels, single use disposals from suppliers."
>
> **— Jon Rowley,**
> *Founder & Chief Product Officer*
> RoosterBio

Case studies from the small molecule and biologic pharmaceutical industry are broadly cited and demonstrate the successful implementation of real time releasing monitoring enabled by integrated manufacturing and multivariable control strategies. Real time release biomonitoring significantly benefits the food and beverage industry by allowing increasing assurance of product safety and quality, while preserving nutritional and organoleptic properties, with improved productivity due to faster market delivery and potentially decreased costs.

Levinson et al., 2018, have described two potential platform designs. The first one consists of a microcarrier-based bioreactor platform focused on the scaling up manufacturing of adherent cell types, typically including mesenchymal stromal cells, human embryonic stem cells and human induced pluripotent stem cells. The second design comprises a modular processing device built to withstand the entire cell therapy manufacturing process including a self-contained unit. According to the authors, both proposed platforms are flexible enough to be substantially adapted to multiple cell types and process variations, while providing consistent results.



Agile Business Models Through Smart Facilities

The race toward the development of breakthrough innovative therapies requires careful business decisions, especially in terms of scalability and quality control. In fact, near the third quarter part of the entire cell therapy biomanufacturing process is associated with quality control. Therefore, biomonitoring solutions play a central role in cell therapy production. According to Harrison et al., 2018, some key takeaways are related to the feasibility of building cell microfactories to provide more agile business solutions, along with an essential need for process automation and quality control diversification in order to afford the cost-burden over larger production batches.

Real time release testing and biomonitoring, mostly as a result of in-line monitoring deployment, holds promise to enhance quality assurance, increase productivity, and reduce cycle times, while delivering collateral potential benefits to the biomanufacturing sector. As a key success factor, real time release testing must be deeply integrated to adjacent enabling technologies, such as life sciences research and nanotech-based approaches, novel biosensing circuits, advanced materials, microelectronics, synthetic biology, and smart robotics, among others. Figure 3 shows a technology radar of intelligent solutions likely to build the future of cell therapy manufacturing.

> "With fourteen thousand doses a year, chain of custody can be an issue."
>
> — **Karen Albertson,** *Global Business Director* 3M

Production Outlook

World Class-Accredited Manufacturing Initiatives

The past five years have showed substantial investment in world class, accredited manufacturing initiatives for both gene and cell therapy manufacturing. While leading manufacturing companies such as Fujifilm, Diosynth, AdaptImmune, Hitachi Chemicals Advanced Therapeutic Solutions, WuXi and AppTec have invested in leasing manufacturing facilities, other companies such as Kite Pharma and Lonza have established new production plants in California and Houston, respectively, looking to expand their manufacturing capabilities. Cell therapy manufacturing is prone to occupy a very active position in terms of the creation of new companies around a highly diversified spectrum of products and services, while constituting one of the most intensive sources of highly skilled employment in the healthcare sector. The need for trained talent is also a key area of unmet need highlighted by the CDMOs.

The most interesting insights came from efforts to uncover the impact of the regulatory landscape governing cell therapy. Overall, the response was very positive, including an outlook that the regulatory authorities are creating an encouraging environment for development of novel therapies. However, there is a perception that there is or is likely to be a CDMO capacity shortfall. This was found more to be a myth or a perception issue in the market, where in reality no shortfall exists. It is likely that such a perception was created owing to the pre-planning and early engagement necessary for transfer of knowledge and for booking production facilities in advance. It was opined that more collaboration between the cell therapy ecosystem can overcome this perception issue and ensure better utilization of capacities at CDMOs.

"The production process is challenging, each step has nuances, like the idea of getting smaller and smaller and personalized production for cells."

— David Smith,
Head of Innovation and Engineering
Therapeutics Solutions

Final Remarks

While capacity shortages at CDMOs was highlighted frequently in the survey and in multiple discussions, the CDMOs were of the view that this is a misconception in the ecosystem. With a little bit of planning and early engagement this notion of "perceived shortage" of capacity can be addressed easily. Collaboration between the CDMOs and the therapeutic players is an absolute necessity as is early engagement with the regulators, payers and hospitals. Building hub and spoke manufacturing models to achieve economies of scale to ensure product consistency is another key strategy that companies must leverage to succeed. Automated closed-loops systems and real time sterility monitoring allowing for Real Time Batch Release will be integrated as core must-have capabilities in the near future. Investments in flexible/ SUT and automation will alleviate some of the current challenges and solutions developed to address these challenges will be very favorably received. Platform solutions around maintaining chain of custody integrity will be crucial as cell therapy growth ramps up.

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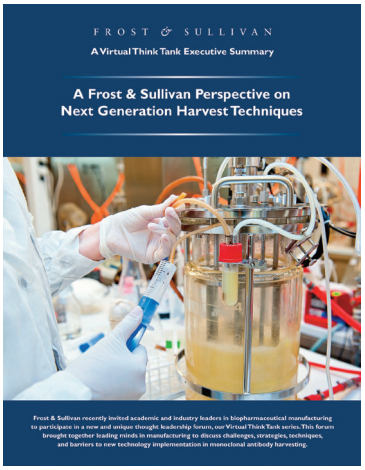
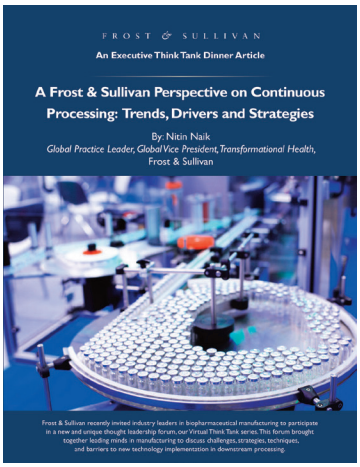


Perspective on Next Generation Harvest Techniques

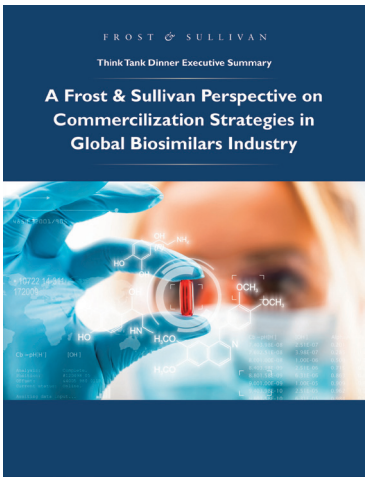
Transition to Next Gen Down-stream Processing to Capitalize on Growth Opportunities in High-Value Low-Volume Biologics

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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