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An Executive Think Tank Dinner Article

A Frost & Sullivan Perspective on Continuous Processing: Trends, Drivers and Strategies

By: Nitin Naik

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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.

Nitin Naik, Global Vice President (GVP) with Frost & Sullivan, opened the discussion by noting that in 2018 the global pharmaceutical industry witnessed a surge in CEO confidence from US tax reforms, turbulent equity markets, and the strengthening global economy. 2019 will continue to see this optimism with a majority of companies committed to build new R&D facilities or manufacturing plants in the U.S.

PANELISTS

- **Hang Yuan**
Senior Director
Shire
- **Joseph DeCoursey**
Head MS&T
Sarepta Therapeutics
- **Aaron Noyes**
Associate Director
Codiak BioSciences
- **Bernhardt Trout**
Professor of Chemical Engineering
Associate Director of DSP
MIT
- **Marcus Fiadeiro**
Continuous Manufacturing
Sanofi
- **Terry Seanard**
Principal Solution Architect
New England Controls, Inc.
- **Alexei Voloshin**
Global Application Strategy Leader
3M
- **Nick Berthelsen**
Global Product Marketer
3M

The US Food and Drug Administration (FDA) released several guideline documents, which are likely to increase the adoption of digital technologies in pharmaceutical manufacturing. These guidelines provided frameworks for electronic submission of clinical data and manufacturing establishment information, while laying down expectations for maintaining data integrity and compliance with good manufacturing practices (GMP).

These guidelines have encouraged pharmaceutical companies to adopt advanced processes such as modular manufacturing, electronic batch record systems and computerized maintenance management systems that employ sensors and advanced analytics. This serves as a great foundation for industry to shift from batch processing to continuous processing.

The discussion began with participants sharing perspectives on evolution of processing strategy and key growth drivers.

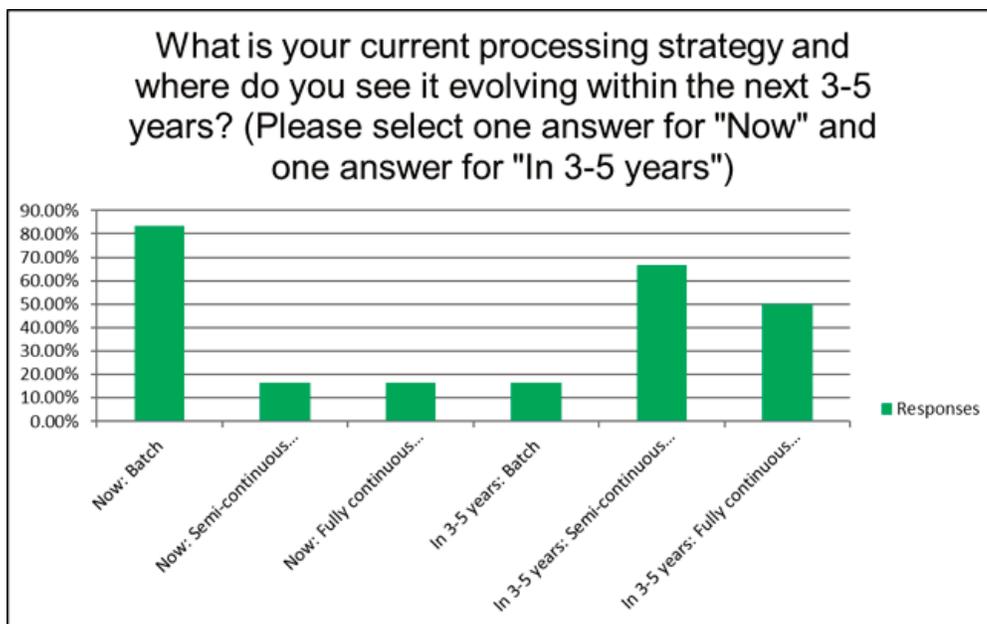


EVOLUTION OF PROCESSING STRATEGY

The race for continuous manufacturing is heating up

Rising payer pressure, the move towards precision healthcare and increasing adoption of digital solutions are key trends shaping the global pharmaceutical industry. To align themselves to these global trends, pharmaceutical companies are optimizing their operations. Adoption of continuous manufacturing and a complete technological transformation are the needs of the hour. The key drivers for this evolution include rising demand for biologics, the desire for reduced processing costs, more stringent requirements for consistent quality, and most importantly, the requirement for higher productivity.

Some of the thought leaders expressed that while batch processing continues to dominate the current scenario, the future clearly lies in semi-continuous processing or fully continuous processing (Figure 1).



KEY GROWTH DRIVERS TO CONTINUOUS PROCESSING

Investing for a Green Manufacturing Future

Continuous processing uses a continuous stream of raw materials, furnishing finished product at a constant rate. Through the use of sensors, an active feedback mechanism reduces the need of manual handling, increasing overall safety in production. The process results in less waste, leading to a lower ecological footprint, and reduced inventory and lower capital costs make the process cost effective.

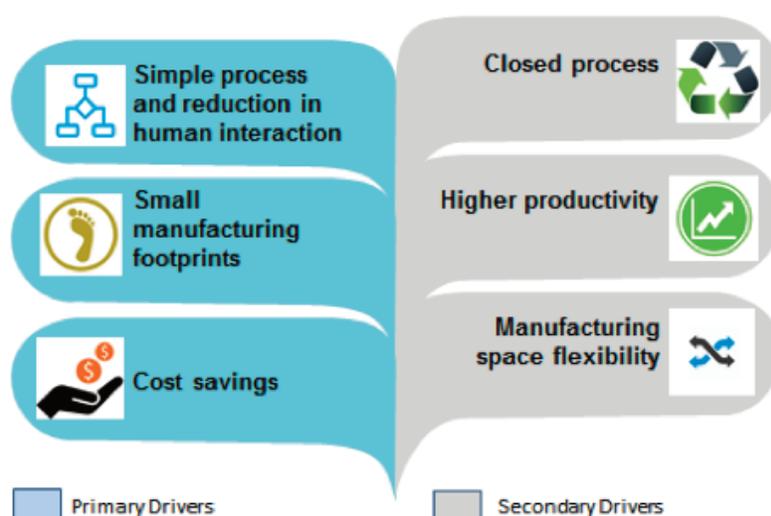
“While platformability can be an important barrier, PAT acquisition that can characterize more bioprocess attributes remains a more potent gap to overcome.”

— Aaron Noyes,
Associate Director
Codiak BioSciences

Janssen's tablet for treating HIV, Prezista, was the first supplemental FDA approval (2016) for changing from an established batch process to a continuous manufacturing process. It resulted in a significant reduction in operational requirements, with the usage of 2 rooms instead of 7 for batch process. Also, production timelines were reduced to 1 day, instead of up to 2 weeks for batch.

The key drivers (Figure 2) for this paradigm shift include the desire for reduced processing costs, more stringent requirements for consistent quality and most importantly, the requirement for smaller manufacturing footprints that could result in simplified processes.

Figure 2: Growth Drivers for Continuous Processing



“Smaller production footprint, cost savings and higher productivity are clear growth drivers. While there are enabling technologies available externally to fulfill the vision of continuous processing, Big Pharma must be prepared to also develop technologies internally.”

Another participant described that "Smaller production footprint, cost savings and higher productivity are clear growth drivers. While there are enabling technologies available externally to fulfill the vision of continuous processing, Big Pharma must be prepared to also develop technologies internally."

“Bernhardt Trout (MIT) pointed out that because effective flow processes are not just reoptimized batch reactions, they present a lot of opportunity for designing new approaches. The strategic approach to process development (PD) is important and difficult, since there are upfront costs, including reallocation of personnel. The PD approach to continuous is different from that of batch. Pharmaceutical companies also need to put more effort into systems modeling. The wonderful thing about continuous processing is that it can help the industry as a whole to cut costs.”

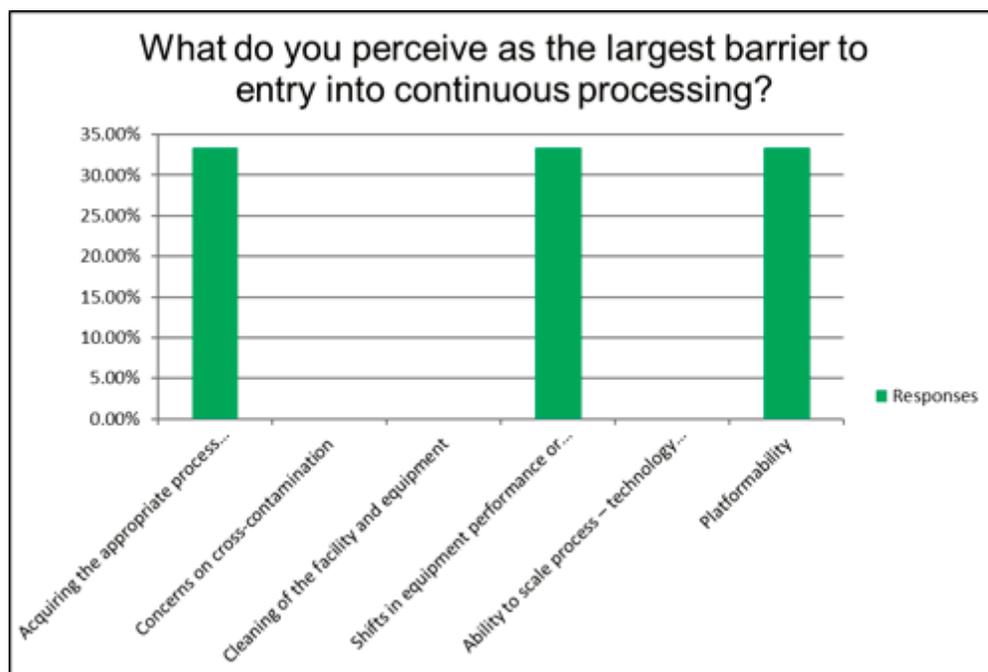
KEY TAKEAWAY:

- Continuous bioprocessing technologies can create significant efficiencies such as heightened capacity and raw material utilization, lower offline quality control and analysis, reduced maintenance and energy usage, resulting in dramatic savings of operational costs.

BARRIERS TO ENTRY INTO CONTINUOUS PROCESSING

Knowing the blind spots around plarformability

Figure 3.0 shows that participants rated acquisition of analytical tools, equipment performance and platformability as the largest barriers to entry.



Aaron from Codiak offered a different sentiment, "Codiak has created a proprietary platform for exosome design and a manufacturing process that allows for precise targeting of molecular pathways involved with human disease. While platformability can be an important barrier, PAT acquisition that can characterize more bioprocess attributes remains a more potent gap to overcome."

Another participant mentioned their organization is currently developing "an integrated and continuous bio-manufacturing (ICB) platform for the universal production of protein therapeutics (antibodies, enzymes, etc.). Integrated Continuous Biomanufacturing (ICB) has multiple advantages for therapeutic protein production through process intensification and integration. We have several proof of concepts that have demonstrated reductions in manufacturing costs by pushing perfusion culture towards high productivity. However, these approaches rely on consistent equipment performance and access to sophisticated analytical tools."

Hang from Shire stated, "Continuous processing has limited upstream applications for scale ranges 500L-2 KL. Feasibility studies around scape up

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— **Bernhardt Trout**,
Professor of Chemical Engineering Associate
Director of DSP
MIT

and PAT have not show good results to justify a strong business case to migrate to this technique. CMC teams in most pharma companies have a conservative mindset compared to clinical and commercial and require a more rigorous capex/opex justification to switch to continuous processing. So platform ability is really biggest barrier."

KEY TAKEAWAY:

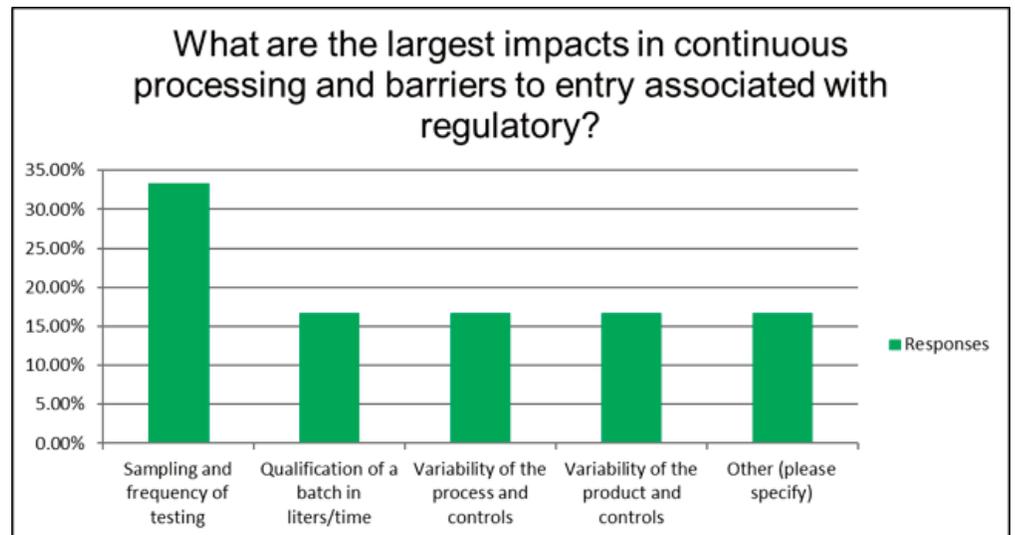
- Continuous processing will require pharmaceutical companies to adopt a holistic manufacturing strategy centered on analytical tools and dashboards capturing new measures of quality and associated metrics.

BARRIERS TO ENTRY ASSOCIATED WITH REGULATORY AND LARGEST IMPACT

Mitigating risks associated with process and product variability. Will the new plan work?

Most participants supported the view that Big Pharma have taken considerable efforts to migrate to continuous manufacturing. As shown in Figure 4, most agreed that the largest impact while making the paradigm shift to continuous processing includes (1) managing sampling and frequency of testing and (2) controlling variability of product or process and controls.

Figure 4



A thought leader at the dinner had this to add, saying “In biologics manufacturing, process is the real product. Big pharma such as Genzyme rely on good cell lines to achieve steady state operations – which are the key advantage (consistent quality, reduced heterogeneity) for continuous processing. Hence sampling and frequency of testing will have the largest impact to deploy continuous manufacturing using risk-based approaches.”

Terry (NECI) commented: “The FDA has been very supportive for industry to pursue a range of strategies designed to improve the flexibility, reliability, and quality of pharmaceutical manufacturing. There are different modeling approaches based on process scale (lab bench, pilot scale, manufacturing scale). From our experience, Hybrid is a better approach. Start with building first-principals and empirical models at the bench scale, then carry those models through and add the statistical models which support equipment variations at the larger scales. This approach provides more control, carries the process understanding through the process life-cycle, and mitigates the risk of process variability on finished product quality.”

Another dinner attendee offered a different perspective, stating, “ICB being relatively new, it requires critical at scale and company-wide manufacturing adoption before it can transform into a mature platform. My organization’s top management has been supportive in making investments to develop this platform and we have gathered nice momentum on integration of upstream and downstream processes. It is imperative to minimize variability of the process or product and controls during integration. It is being done but can be tedious.”

KEY TAKEAWAY:

- Evolving regulatory guidelines, gaps in technical expertise and system complexities for both small and large molecules remain key hurdles. There is a wide variety of next generation bio-filtration technologies being developed that can ensure the application is fit for purpose and the final outcome is a robust solution.

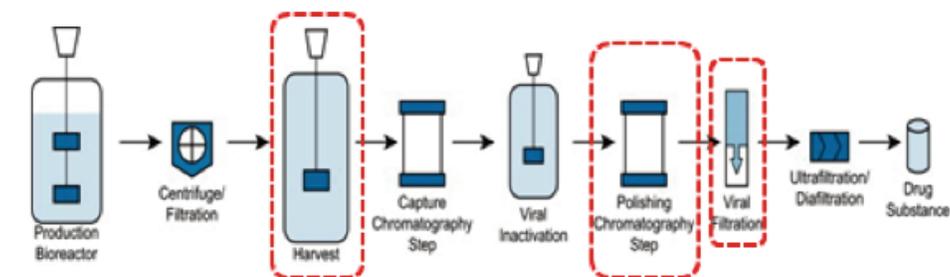
BOTTLENECKS & PURIFICATION TECHNIQUE CHANGES NEEDED TO FIT WITH UPSTREAM & DOWNSTREAM CONTINUOUS PROCESSING

Downstream processing operations at a turning point

Nitin continued the conversation by highlighting that increasing expression levels in cell culture and implementing upstream processes has caused downstream purification to become a “bottleneck” in biologics manufacturing. New approaches such as integrated downstream processes with multi-column chromatography have shown incredible results with

increased throughput and reduced capital and operational expenses. All participants strongly debated the inter-relationships between bottlenecks and purification technique changes needed to fit with downstream continuous processing (Figure 5 below)

Bottlenecks & Purification Technique Changes to fit with Downstream Continuous Processing



Top 3 Bottlenecks

1. Polishing chromatography steps
2. Viral filtration
3. Harvest/clarification



Top 3 Purification Technique Changes

1. Continuous chromatography capabilities
2. Pool-less integrated processing (polishing)
3. Platformability

Graphic source: Science Direct

Another thought leader commented, "The influence of variability in upstream processes on continuous TFF operations needs to be demonstrated. In my view, viral filtration can be the biggest bottleneck as specific challenge tests are needed for validation. Polishing chromatography steps is the least concern amongst other listed bottlenecks. In response to changes to purification techniques he added, "Integrating multi column chromatography is a good business case. This change has demonstrated an increase in product quality, lower COGS and has being easy to replicate."

Alexei from 3M noted that "Most large molecule purification processes involve an affinity-based chromatography step. However, a significantly higher (>90%) purity of Protein A-eluted product with respect to DNA and HCP is insufficient, and a complex and expensive polishing train is still required. The industry should evaluate new generation of absorptive filters for product purification processes, and explore their effect to obtain higher concentrations pools prior to virus filtration and ultra/diafiltration."

KEY TAKEAWAY:

- Upstream processing is no longer a bottleneck with titer expressions surpassing 10 g/L. First capture step continues to be a key challenge in downstream processing. New downstream approaches are needed that retain coherent biological, chemical and physical characteristics of molecules, in particular the new generation of biologics and biosimilars

Conclusion

The era of biopharmaceuticals and targeted therapies ushered in the age of precision healthcare. Better understanding of disease heterogeneity and identification of disease targets has fostered collaboration between pharmaceutical companies, bio-filtration systems manufacturers and CDMOs to launch new drugs for treatment of oncology, cardiology and metabolic diseases.

This phenomenal infrastructure has established a solid launch pad for continuous processing technologies to gain critical mass and enable a highly responsive ecosystem that can pivot around real-time monitoring and quality control, optimized decision making, reduced costs, and improved patient outcomes.

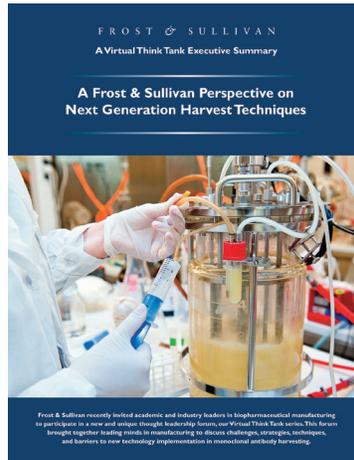
There was a consensus to adopt the following strategies to be successful in the transformational journey to adopt fully continuous processing:

- **Biologics - clear sweet spot:** Capital and operating expenses for biologic plants greatly exceeds those of small molecules. The increasingly stringent regulations with manufacturing, particularly mammalian-based manufacturing, is expected to increase cost of manufacturing thereby creating a high entry barrier and making it unsustainable for small manufacturers. Keeping in mind this challenge, pharmaceutical companies need to think of innovative ways of collaboration with bio-filtration manufacturers to adopt continuous processing technologies.
- **Regulators-build partnerships to win:** Regulatory agencies are encouraging manufacturers to transition to continuous manufacturing. The FDA was one of the first regulatory agencies that recommended adoption of continuous manufacturing. The European Medicines Agency (EMA) has adopted a similar stance and recommended early dialogue with the agency, especially for legacy products transferred from batch to continuous manufacturing.
- **Process analytical tools enabling new value based care outcomes:** During the last 5 years, regulatory agencies have put across a comprehensive framework and numerous guidelines to support the pharmaceutical industry's adoption of continuous processing technologies. Manufacturers need to construct analytical tools to measure critical process parameters (CPP) and critical quality attributes (CQAs) and devise control strategies to support implementation of downstream continuous processing. Control strategies designed for batch mode on bench top scale can be phased into continuous processing.

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



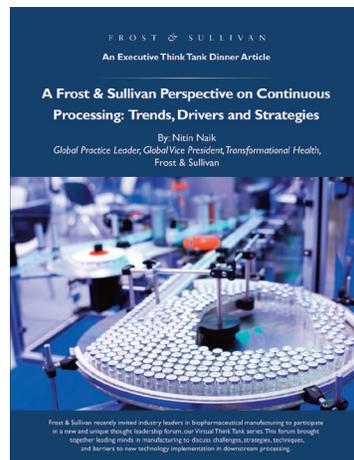
Perspective on Next Generation Harvest Techniques



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



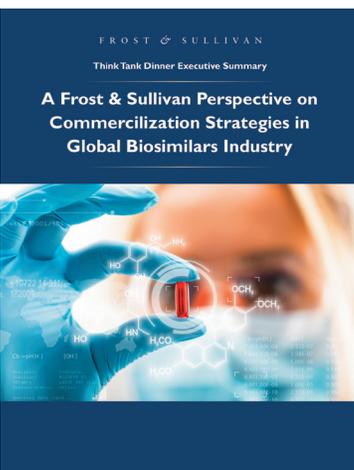
Enabling Novel Bioprocessing Technologies Using the Interface of Materials Science Biotechnology



Perspective on Continuous Processing: Trends, Drivers and Strategies



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