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Think Tank Dinner Executive Summary

A Frost & Sullivan Perspective on Commercilization Strategies in Global Biosimilars Industry

MODERATOR

- **Nitin Naik**
  Vice President, Global Life Sciences
  Frost & Sullivan

THOUGHT LEADERS

- **Alexei Voloshin**
  Global Application Strategy Leader - Separation and Purification Sciences Division
  3M
- **Andrew Sandford**
  Vice President, Global Business Development - Biologics
  Catalent Pharma Solutions
- **Arvind Srivastava**
  Vice President
  Avantor
- **Himanshu Nivsarkar**
  Global Marketing Manager
  3M
- **Howard Levine**
  President and CEO
  BioProcess Technology Consultants, Inc.
- **Karen Albertson**
  Global Life Science and Integration Director
  3M
- **Maria Cho**
  Senior Director Commercial Development
  FUJIFILM Diosynth Biotechnologies
- **Mark Yang**
  Director, Global Pharmaceutical Development Biologics
  Sanofi

A FROST & SULLIVAN PERSPECTIVE ON COMMERCIALIZATION STRATEGIES IN GLOBAL BIOSIMILARS INDUSTRY

Frost & Sullivan recently invited industry leaders in biopharmaceutical manufacturing to participate in a new and unique thought leadership forum, our Executive Think Tank Dinner. This forum brought together leading minds in manufacturing to discuss key trends, challenges and success factors in global biosimilars industry.

Nitin Naik, with Frost & Sullivan, opened the discussion by noting that Frost & Sullivan analyst team put a stake in the ground around mapping commercialization challenges back in 2015. He went on to explain key commercialization considerations by offering the following Frost & Sullivan definition:

"A biosimilar is a biologic that is "highly similar" to an approved biologic (or reference product) that is already being used to treat patients. The goal of a biosimilar development program is not to re-establish the safety and efficacy of the product, but rather to demonstrate that the biologic product is biosimilar to the reference product. It is generally understood that there are acceptable variabilities between the biosimilar and the branded reference product, and an approved biosimilar will have no clinically meaningful differences from there ference product in terms of efficacy and safety.

The discussion began with participants sharing perspectives on key growth drivers and regions that present greatest potential.

GROWTH DRIVERS

Patent Expiries propel growth

Every participant detailed their experiences around regulatory approval pathways and patent expires on major biological products. While there was a consensus that patent expiries (Figure 1) will opens the opportunity for biosimilars to enter the market and increase competition among producers of biologics, participants debated that the growth trajectory would be different in US and European markets.

Figure 1: Key Biologics Patent Expiry
Major Biological Patent Expiries: Europe and US (2010-2020)

Europe

Segment	Product / Molecule	Patent Expiry
mAbs	Herceptin®	2014
	Avastin®	2022
	Remicade®	2015
	Rituxan® / Mabthera®	2013
	Humira®	2018
	Enbrel®	2015
Insulin	Lantus®	2014

US

Segment	Product / Molecule	Patent Expiry
mAbs	Rituxan®	2016
	Humira®	2016
	Xolair®	2018
	Erbitux®	2018
	Remicade®	2016
	Avastin®	2019
	Herceptin®	2019
	Enbrel®	2028
Insulin	Lantus®	2014
	NovoMix® 30	2017
	Levemir®	2019

A recent Frost & Sullivan survey pointed that while patent expiry is great opportunity, patients & physicians lack of trust necessitate significant market development activities. In the past, few players have exited this marketon the basis of significant financial commitments required to compete in the long run.

One panel member described that "Biosimilars are currently in clinical use in all EU states. Despite a slow initial uptake, government incentives will continue to propel industry growth in next 5-10 years". As per the latest estimates by Frost & Sullivan, the introduction of biosimilars in eight European countries (Germany, Italy, Spain, France, Romania, UK, Sweden, and Poland) will generate savings of about ∈33–37 Billion by 2020.

KEY TAKEAWAYS:

- Key therapy areas such as oncology (mAbs), diabetes (insulin), and rheumatoid arthritis (mAbs) will spearhead biosimilar growth during 2019 through 2022.
- Efficacy, safety issues, and interchangeability or substitution practices remain key concerns, especially in the U.S. market.

- **Mark Emalfarb**
  Founder, Chairman and CEO
  Dyadic International, Inc.
- **Mark Gehlsen**
  Global Technical Director
  3M
- **Mike Ultee**
  Principal
  Ulteemit BioConsulting, LLC
- **Modestus Obochi**
  Strategy & Business Development Advisor
  Pfenex Inc.
- **Nandu Deorkar**
  Vice President, Technology and Innovation
  Avantor
- **Nick Vrolijk**
  Vice President Manufacturing Operations
  Celldex Therapeutics
- **Patrick Lucy**
  Chief Business Officer
  Pfenex Inc.
- **Paul Jojorian**
  Head of BioProcess Sciences
  Thermo Fisher Scientific
- **Dr. Sarfaraz Niazi**
  Founder
  Pharmsci KaryoBio AdelloBio
- **Sigma Mostafa**
  Vice President, Upstream & Downstream Process Development
  KBI Biopharma
- **Stacie Ropka**
  Partner
  Axinn, Veltrop & Harkrider LLP

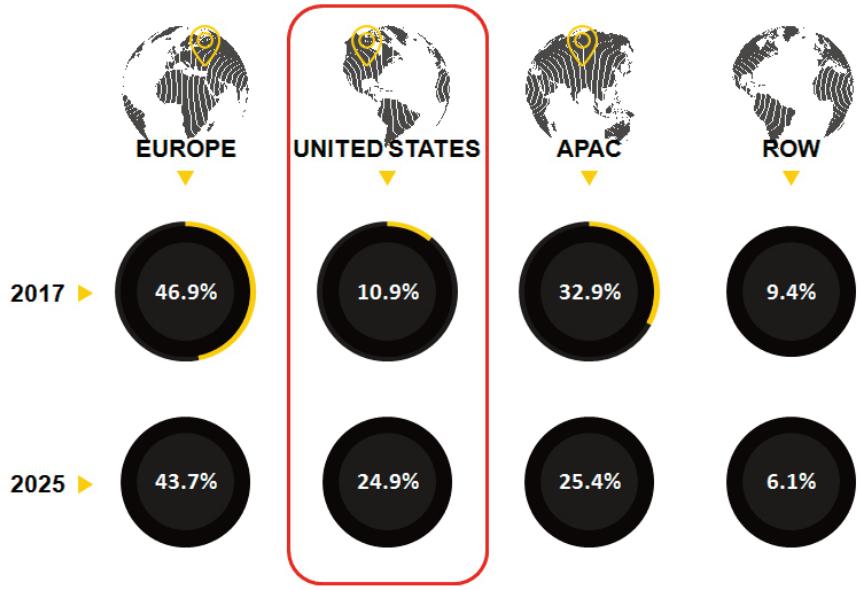
"Biosimilars are currently in clinical use in all EU states. Despite a slow initial uptake, government incentives will continue to propel industry growth in next 5-10 years."

REGIONS/COUNTRIES WITH GREATEST POTENTIAL

Unlocking potential in Americas

Some of the thought leaders expressed that while Europe will continue to dominate the global market, US will see rapid growth due to changes in regulatory landscape (Figure 2).

Figure 2: Total Biosimilars Market:
Percent Revenue Forecast by Region, Global, 2017–2025



Current contrasts in the utilization of biosimilars across European markets reflect variations in the local reception of treatment practices and rules impacted by financing decisions and payer activities. Germany, Denmark, and the Netherlands, have introduced various incentive programs and established strategic models for discount pricing and rebates.

Remicade's biosimilar Remsima has been commercialized in Europe since 2014. Remsima started its sales in Europe with a 39 to 40 percent discount from the list price of Remicade and captured 6 to 7 percent of the market in 2014. But in 2015 to 2016, the discount rose to almost 70 percent, thus supporting increase in market share to as high as 45 to 50 percent of the Remicade market.

Stacie (Axinn) pointed that the follow-on biologic market in the United States is different from the market in Europe. Unlike Europe, in the United States there are two categories of follow-on biologic. There is the interchangeable biologic, which can be automatically substituted for the reference product at the pharmacy. Although no interchangeable followon biologics have been approved by the FDA, it is likely that once they are approved and available, the market will form. The other category is the biosimilar follow-on biologic, which must be specifically prescribed by the physician. Thus, physicians must be aware that biosimilar follow-on biologic is available and must be comfortable in prescribing the biosimilar.

She further expanded that educating physicians and patients has just begun with informative videos from the FDA and will also likely include marketing by the pharmaceutical companies who are selling follow-on biologics. Physician and patient by-in will drive how quickly and completely the biosimilar follow-on biologic market will form.

Dr. Niazi (Karyo Biologics) commented, "There is no doubt US will emerge as largest market within next 10 years. Currently there are only 12 products approved; all from Big pharma and none from smaller biotech companies. So biotech have a great opportunity to disrupt this market. This will require a unconventional mindset that requires partnerships with distributors and specialty pharmacies for whom this is a miniscule business at this point."

Ms. Sigma (BPI Pharma) added, "Initially both developed and developing countries with good bio-manufacturing capabilities rushed into this market. However high capex investments and regulatory challenges have pushed back their ambitious plans". To overcome these challenges, many companies have partnered with CDMOs to get a foothold in the market.

KEY TAKEAWAYS:

- More than 800 companies globally are actively developing biosimilars with Europe currently leading in terms of biosimilar manufacturing volume. S.Korea, China & India have made significant capacity investments and have potential to surpass Europe in next 5-7 years.
- Physicians, patients at center stage as prescription and usage rates are linked to ROI models

IMPACT OF CURRENT AND FUTURE REGULATORY LANDSCAPE

IP strategies to work around market exclusivity

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> **— Dr. Sarfaraz Niazi**
> *Founder*
> Pharmsci KaryoBio
> AdelloBio

> "Biosimilar companies face steep challenges on both the commercial and legal frontiers for their products. Their development cost curve is similar to innovators so it will be difficult for them to compete on price like traditional generics, especially without substitutability."
>
> **— Howard Levine**
> *President and CEO*
> BioProcess Technology Consultants, Inc.

The regulatory policies governing biosimilars are still evolving, with markets like China lacking clear approval pathways. The United States issued draft biosimilars guidance in 2013 but many questions regarding market exclusivity, labeling of interchangebale products, patenting is yet to be completely resolved.

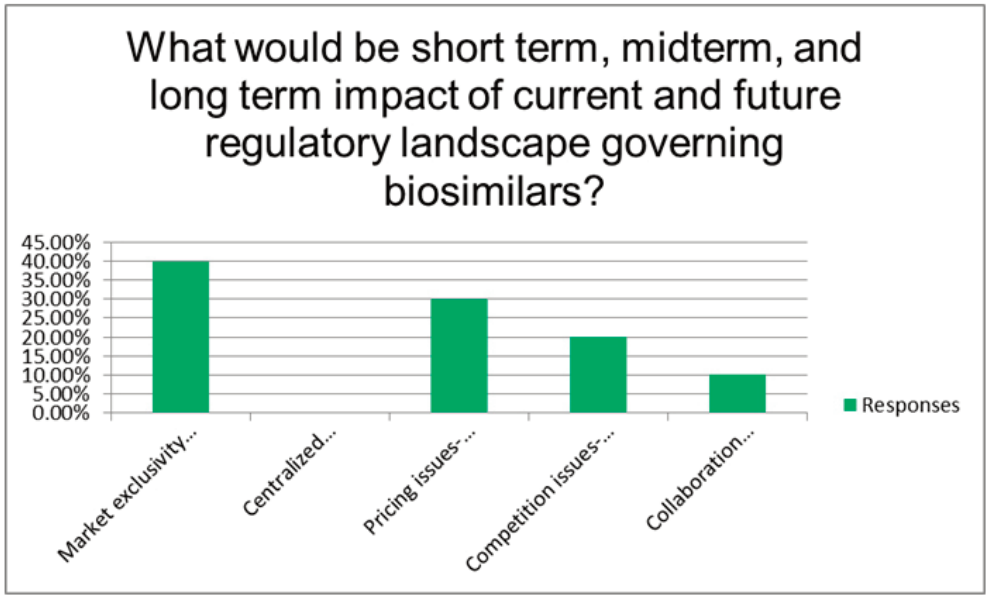


Figure 3.0 shows that panelists regarded exclusivity, pricing and competition as most critical issues.

According to the Association for Accessible Medicines (AAM), exclusivity period for biologics in the USA (12 years) is longer than in any other country in the world. Europe has the second-longest exclusivity period, generally providing for ten years of market exclusivity; Canada's biologic exclusivity period is eight years. Other countries permit just five or six years of market exclusivity.

Dr. Howard Levine (Bioprocess Technology Consulting) explained: "Biosimilar companies face steep challenges on both the commercial and legal frontiers for their products. Their development cost curve is similar to innovators so it will be difficult for them to compete on price like traditional generics, especially without substitutability." He further noted that "commercialization routes for each therapeutic indication is very different so that in some indications, like oncology, biosimilar companies may struggle to be profitable in short to midterm if they cut costs significantly to gain market share."

Patric and Modestus from Pfenex offered a different sentiment, "While managing interchangeability requires a sophisticated commercial and IP strategy, it is the politics surrounding interpretation of interchangeability that will limit US market growth".

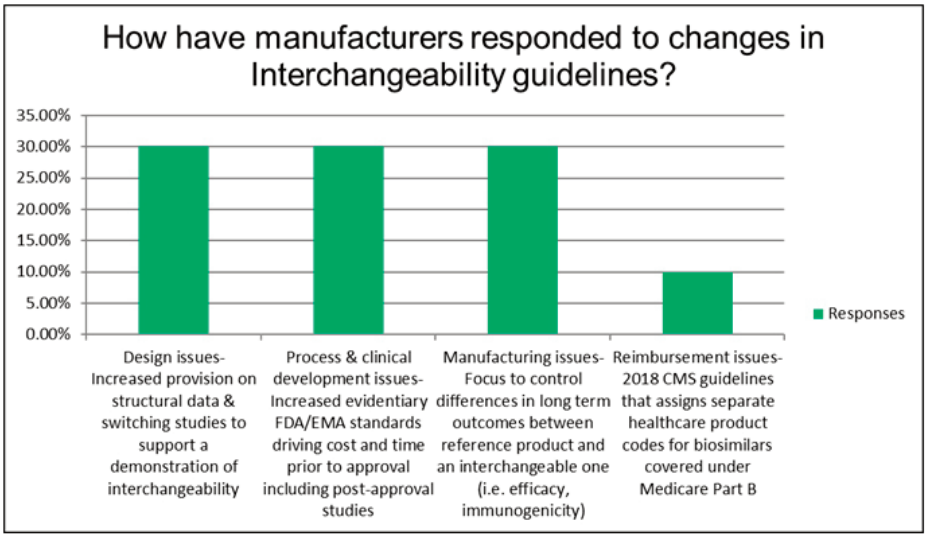
KEY TAKEAWAYS:

- The interchangeability guidelines in US are misguided on some fronts. FDA determines interchangeability but state boards of pharmacy control substitution.
- Efforts to advance the use of biosimilars have been more successful in Europe where more than 40 biosimilars have being approved compared to around 13in US.

MANUFACTURER'S RESPONSE TO INTERCHANGEABILITY GUIIDE LINES

Process development and manufacturing issues govern development programs

Nitin opened the conversation by highlighting two key considerations for biosimilar companies (i) Design issues- increased provision on structural data & switching studies to support a demonstration of interchangeability (2) Process & clinical development issues- Increased evidentiary FDA/EMA standards driving cost and time prior to approval including post-approval studies.



Most participants agreed that set bar for biosimilar interchangeability is pretty high and it will significantly increase the cost and time of clinical development prior to approval.

Paul (Thermofisher) said: The perspective of our customer is very similar to graph in the survey booklet. Very interesting indeed!

Maria (Fujifim Biotechnology) commented: "My belief is that the competition levels in this industry will be extremely high. Most biosimilar companies may not able to match innovators on product quality, costs and brand loyalty. In this industry, process is product and so the real innovation revolves around molecule design issues and clinical switching studies. Until more pharmaco vigilance data is compiled, questions about appropriate product quality attributes will restrict switching."

Sigma (BPI Pharma) offered a different perspective: "We work with both innovators and biosimilar companies. In emerging markets, approval processes are speedier than in developed markets, with less stringent comparability criteria. Biosimilar companies in this region have adopted aggressive process and clinical development plans to move quickly into commercial manufacturing."

KEY TAKEAWAYS:

- Major challenges to the adoption and effective utilization of biosimilars include timing, interchangeability and pharmacovigilance
- The lacks of clear guidelines on substitutability will likely cause physicians to exercise caution in prescribing biosimilars until they gain comfort with the quality and efficacy of biosimilars.

"We work with both innovators and biosimilar companies. In emerging markets, approval processes are speedier than in developed markets, with less stringent comparability criteria."

— Sigma Mostafa
Vice President, Upstream & Downstream Process Development
KBI Biopharma

"While Biosimilar companies have developed extensive manufacturing capabilities, current interchangeability guidelines pose challenges to clinical development. The most relevant example is for oncology therapeutics settings where recruitment of patients is so difficult let alone testing them on biosimilar products."

— **Dr. Sarfaraz Niazi**
Founder
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UNIQUE CAPABILITIES & STRATEGIES OF MARKET PLAYERS

Clash of global titans brewing in Europe and emerging markets

The increasing number of biosimilar approvals in emerging markets as well as the financial strength of the big pharmaceutical and generic companies is reasons for the emergence of new market participants. In particular, Asian participants such as Celltrion, Biocon, Samsung Bioepis, and Wuxi Biologics have aggressively entered the global markets and challenged multinational companies (Figure 5 below)

Asia-Key Companies to Watch

Samsung Bioepis	Biocon	Wuxi Biologics	Celltrion
Samsung Bioepis is a leading global player in biosimilars based in Korea. In just two years, Korea's Samsung Bioepis gained European regulatory approval for four biosimilars(BS), setting an Industry record.	Biocon, an Indian company, is a major biosimilar participant. Biocon has an exclusive partnership with Mylan on a broad portfolio of biosimilars and generic insulin analogs.	Wuxi Biologics is building an integrated, single-source, open-access capability and technology platform to enable anyone and any company to discover and develop Biosimilars. It has plans to add 30,000L of capacity progressively	Celltrion, a Korean company, has patents around different types of cell lines that it has modified, as well as formulation and biomolecule characterisation. It has emerged as global leader with multiple biosimilars in their pipeline.

Nitin challenged the panelists by probing if originator and biosimilar companies can play this game together to improve patient access.

Dr. Niazi (Karyo Biologics) commented, "There are three types of players who compete with an unique mindset in this space; Innovators (pure play companies), Innovators turned biosimilar companies and Biosimilar companies. While Biosimilar companies have developed extensive manufacturing capabilities, current

interchangeability guidelines pose challenges to clinical development. The most relevant example is for oncology therapeutics settings where recruitment of patients is so difficult let alone testing them on biosimilar products".

Andrew Sandford stated: "Innnovator companies developing a biosimilar version of their own innovator product have an established strong position in market. Unless the biosimilar companies can access market share quickly, these innovators are likely to retain their advantage. Biosimilar companies also risk going out of business if they can't sustain the development costs or raise capital quickly. But there are some clear sweet spots for biosimilar companies."

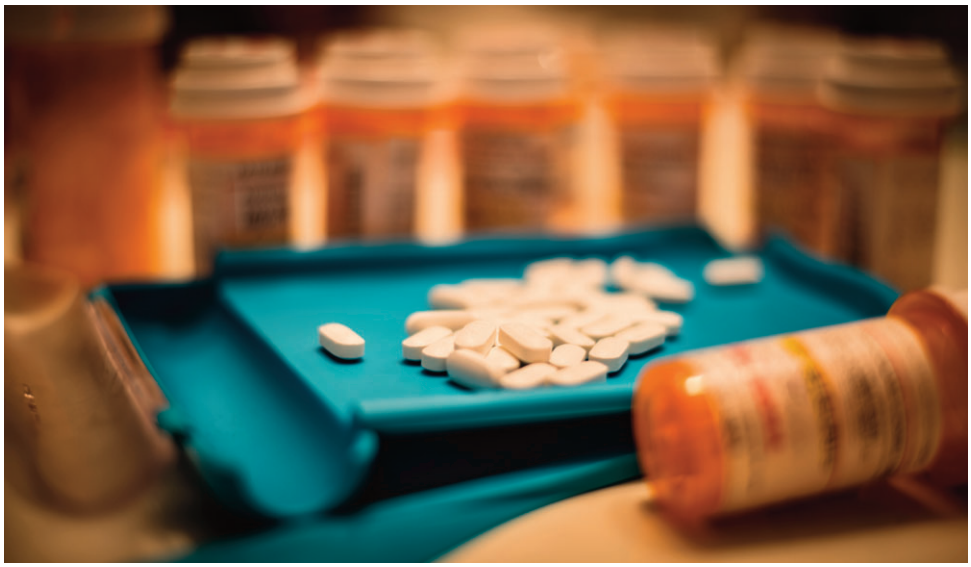
Another participant spoke in a similar vein: Innovator companies have all the pieces in place to go after the biosimilar markets. With a distinguished value proposition, this as perfect storm to ride out in long term."

KEY TAKEAWAYS:

- Asian companies have demonstrated leadership to identify drugs with greatest potential, develop clinical programs based on patent expirations and established extensive capacities. Their investments to develop newer biochemical assays and modifications due to new Chemistry, Manufacturing and Controls (CMC) requirements by both FDA and EMEA will provide them an unique competitive advantage.
- Innovators have amplified efforts to increase market access building on the demonstrated efficacy of their products and their established history within the market. They have an intrinsic advantage within the market to leverage physician and patient trust.

COST TARGETS OF BIOSIMILAR DEVELOPMENT

A double edged sword?



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— Andrew Sandford
Vice President, Global Business Development - Biologics
Catalent Pharma Solutions

> "Product specifications are required to be established early in the development cycle (upstream process) to release manufacturing lots that can be used in analytical comparability and clinical studies to assess biosimilar stability."
>
> — **Sigma Mostafa**
> *Vice President, Upstream & Downstream Process Development*
> KBI Biopharma

Prioritizing new processes and technologies can be the most impactful to enhance biosimilar companies' manufacturing operations. Nitin outlined survey response which pointed out that establishment of comparison metrics with reference product and marking out quality target product profile (QTPP) early in the development cycle stand out as clear game changers.

KBI pharma's strategic imperative has being to enhance process development capabilities including full process characterization and design of robust processes that are almost "phase III like" at phase I. Expanding on this point, Sigma at BPI pharma explained, "Product specifications are required to be established early in the development cycle (upstream process) to release manufacturing lots that can be used in analytical comparability and clinical studies to assess biosimilar stability. This information will be mostly based on analytical data accumulated from the analysis of the reference product. We have to get lot more done and work with different CHO lines to see what works the best. Upstream development is really at"heart" of the cost prediction.

Andrew (Catalant Biologics) commented: "It is more about know-how and where you start from. Multiple methods and approaches are required to characterize biologics. Comparison is the fundamental premise of biosimilar development – and therefore is different from new drug development. Hence, the tools in your toolbox at the start of biosimilar development are more important".

KEY TAKEAWAYS:

- Biosimilar companies must define the QTPP to highest level of resolution as technically feasible.
- Comparison should include the totality of evidence across multiple dimensions of the product (drug product attributes, impurity profile etc)

INNOVATIONS IN UPSTREAM &DOWNSTREAM MANUFACTURING

Market access supersedes technology innovations

Most biosimilars have a 7-10 year development time line with $ 100-$200 million investment. In order to compete with innovators on price, biosimilar companies have to manage both upstream and downstream process manufacturing extremely well.

Selecting a cell line with high productivity will yield the highest amount of titer in each bioreactor run. Similarly an efficient downstream process to purify the biosimilar from the crude cell harvest will make a significant impact. Both ultimately drive efforts of biosimilar companies to establish comparability and match CQA to reference products. Are there other disruptions on the horizon to this established base line winning formula?

Nitin outlined the current landscape; "With heavy competition, optimizing manufacturing costs is critical for all biosimilar companies. Most players leverage operational excellence techniques to maximize cost-effectiveness within their size/scale."

Paul (thermo fisher) noted. "Drug Substance manufacturing costs typically account for 5-10% of overall costs. There is a wide range of manufacturing cost estimates (typically $ 100/gram-$500/gram). Cost variations are inversely proportional to scale, but with titer improvements, the need for massive scale production decreases. If you double your titer, you're producing twice as much in the close to the same cost".

When asked the question about deploying alternative to protein A platforms in downstream manufacturing, Mike Ultee (Ulteemit Bioconsulting): Protein A is very well established and not too expensive. There are more innovations in upstream processing that downstream processing!

KEY TAKEAWAYS:

- Costs of goods/manufacturing are much less important to abiosimilar company than building a integrated market access strategy.
- Many biosimilar companies prefer single-use facilities as they are more cost-effective vs. large-scale stainless steel facilities. Most have also partnered with a competent CMO to achieve increased speed-to-market or lower initial capex.

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> Frost & Sullivan

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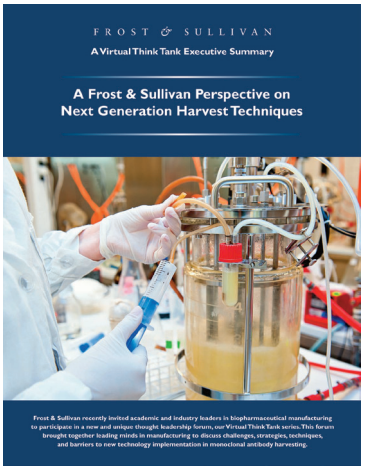
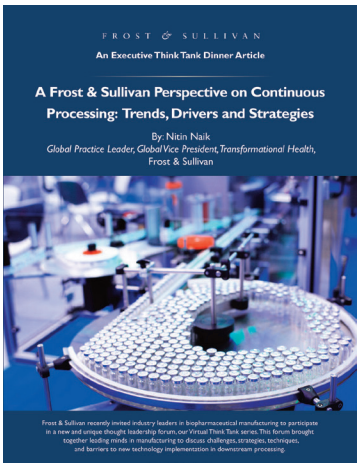
Key Trends Reshaping The Future of Bio-pharmaceutical Harvest and Clarification



Perspective on Next Generation Harvest Techniques

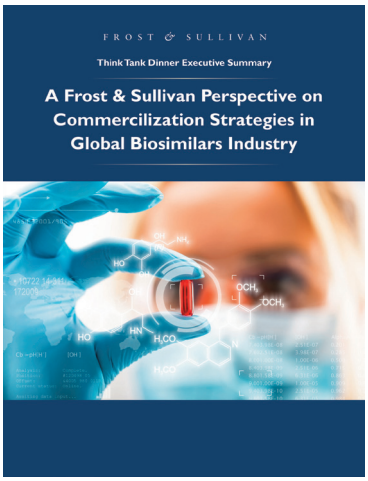
Transition to Next Gen Down-stream Processing to Capitalize on Growth Opportunities in High-Value Low-Volume Biologics

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



Commercialization Strategies in Global Biosimilar

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