Issue Date: June 2012 BP Special 25th Anniversary
2000 words (Actual 2680)
BioPharm International
Editor Contact: Angie Drakulish, Sr. Managing Editor, adrakulich@advanstar.com

Description: Retrospective + prospective view of biopharma that has emerged over the past 25 years; forward looking piece based on input from our Biotechnology Industry Council's 275 different opinions

_____

25 Years of Biopharma Industry Growth

What a difference a quarter century makes

The biopharma industry remains a vibrant and exciting segment, partly because of the promise it holds for a better future for each of us. Much of the energy comes from the dedication of this industry's participants: from its inventors, to its managers, to its innovative suppliers.

Twenty-five years may seem a long time, but many of the 275 industry experts represented in BioPlan's *Biotechnology Industry Council™* have been in the field for that time span, and have dedicated their careers to meeting the challenge, so we take a moment to hear directly from the industry experts about what's changed over that time, and where they see the promise and opportunity for the future. We relate these perspectives from our industry experts, to trend data from our recently released, *9th Annual Report and Survey of Biopharmaceutical Manufacturing*.

The Past 25 Years: Landmark Advances, and Industry's Perspective

We asked the industry, represented by our 275 Biotechnology Industry Council™ participants to define the evolutionary changes that have occurred over the past 25 years. Although we found great depth and diversity of answers from this industry's senior Subject Matter Experts, they all generally focused on the dramatic increases in productivity resulting from improved processes, higher titres, and in particular, the enabling changes that have resulted from the introduction of single-use devices. Below are representative comments on the past 25 years of change in biomanufacturing:

Without question, it is the change in expression systems and cell substrate diversity….engineering, design, clonal selection, and metabolic engineering. We have witnessed multi-fold improvements in product titers, yields, and productivities, across a wide range of products (therapeutic proteins and vaccines). It was the engineering *inside the cell* that has been the driver in bioprocess innovation.	***Jose Manuel Otero, Manager/Group Leader, Upstream PD, Merck***
The phenomenal increase in titers (mainly antibodies) with mammalian cell cultures.	***Dr. Ajish Potty, Development Engineer III, Process Solutions, EMD Millipore***

Emergence and maturation of mammalian cell culture as a product supply option. It has gone from struggling with low titers in the early days to stable cell lines producing several grams/L out of the gate!!!!	***Anonymous, Director, Global Bio/Pharma***
Better understanding of bioprocess requirements [resulting from] dedicated facilities, to product dedicated process trains, to (truly) multi purpose facilities. As well as the quantum leaps in product titers.	***Hans Engels, President and CEO, DSM Pharmaceuticals, Inc.***
Use of disposables in large scale manufacturing. 20 years ago everything was stainless steel. The difference now is astounding. I have worked in plants that are 100% disposable…This has led to decreased production times (even with the increases in titer). It will advance the industry by creating more opportunities for contract manufacture of biosimilars and bio-betters since plants will be simpler to build and validate using QbD.	***Michael Larson, Downstream Process Development, CMC Biologics***
Strain optimization and advances in genomics and proteomics made hard to produce proteins available for human use. Use of disposables reduced capital investments in hard-steel.	***Semsi Ensari, Associate Director, Process Development – Upstream, Ambrx***
Increased standardization of Bioassays. Validation parameters have become more stringent. There has been movement for harmonization when the same assay is performed at multiple sites.	***Janet Lathey, Director, Immunology and Assay Validation, Emergent BioSolutions***
The emergence of single-use technologies.	***Bruce Rawlings, Senior Marketing Manager, Allegro SUS, Pall***
Automation of manufacturing and formulation processes have completely changed the biomanufacturing arena and contributed to reducing cost and increasing yield.	***Eric Halioua, CEO, Promethera Biosciences***
The explosive increase in cell culture productivity.	***Sourav Kundu, Director, PD, Amgen***
Removal of animal-derived components from all aspects of production of biologics.	***Dr. Denny Kraichely, Associate Director and CMC Team Leader, Portfolio Mgmt, Janssen***
Several dramatic changes: The migration of downstream bioprocessing from the cold room to room-temperature processes; The 100X increase in protein titers in cell culture; and Advances in single-use technologies and their acceptance across the board in bioprocessing.	***Dr. Michel Ultee, CSO, Laureate Biopharmaceutical Services, Inc.***
The rise and fall of reusable hardware in upstream bioprocessing and the takeover by disposables (both upstream and downstream). The effects on the industry have been truly profound.	***Dr. John Morrow, Jr., Newport Biotech Consultants***
The change from lack of bioreactor capacity to a glut of bioreactor capacity and idle facilities, due to the dramatic increase in cell culture titers.	***Jeffrey C. Johnson, Engineering Dir, BioVaccine Process Engineering, Merck***
Single use and disposable technologies have allowed process economics to play a major role in system design.	***Michael LaBreck, Global Product Manager, TangenX TFF Products, Novasep***

Single use equipment.	***Dr. Fausto Vellani, COO, Cerbios-Pharma SA***
The transition from highly specialised processes performed within a small number of specialist companies in equally specialised facilities, to those performed on a worldwide basis in all continents, with major growth areas outside the US and EU. From a processing perspective, the significant increases in process productivities for Mab systems. Additionally, the adoption of single use technologies over the last 10 years has reduced the cost and time of getting products into clinical trials.	***Tony Hitchcock, Head of Manufacturing Technologies, Cobra Biologics***

The Next 25 Years of Biomanufacturing

Perhaps more importantly, we also wanted to understand how these global experts felt biomanufacturing will change the industry over the next 25 years. Many see the improvements in biomanufacturing today as having a profound effect on global healthcare. Improved manufacturing will permit greater global accessibility to drugs, will dramatically reduce manufacturing costs, and will ultimately increase the overall number of biological products going into clinical trials. Thus, the changes and improvements in manufacturing operations today are being directly translated into improvements in how patients will be treated over the next quarter century.

Below are representative comments on how the current trends will affect us over the next 25 years:

The focus [will continue to be] on consolidation, and a renewed focus on designing robustness (e.g., QbD, PAT) and being able to deploy processes to all parts of the globe. This means bioprocesses will be simpler, smaller, disposable, requiring minimal utility and energy inputs, while capable of standing up to increased regulatory and quality requirements.	**Jose Manuel Otero, Manager/Group Leader, Upstream PD, Merck**
Higher titers are transforming the way we do and think about downstream purification and will continue to drive innovation in this area.	**Dr. Ajish Potty, Development Engineer III, Process Solutions, EMD Millipore**
Industrialization of Antibody-Drug Conjugate products. I expect to see many more products in this class on the market in the next 25 years – with indication expanding well beyond traditional oncology applications.	**Anonymous, Director, Global Bio/Pharma**
Biotech products [will become] more affordable. Addressing the needs of the patients by producing (affordable) products for smaller segments and further optimizing and standardizing the unit operations.	**Hans Engels, President and CEO, DSM Pharmaceuticals, Inc.**
More products on the market much more quickly. Hopefully we will address the waste management of all of these "disposable" items. There are opportunities for advances to be made in recycling technology as we address this issue.	**Michael Larson, Downstream Process Development, CMC Biologics**
The cost of human health care will reduce with increased productivities and highly efficacious products coming out of these advances. Green manufacturing will be part of new human health care with expansion of eco-friendly disposable use.	**Semsi Ensari, Associate Director, Process Development – Upstream, Ambrx**

The standardization and harmonization of vaccines will allow us to better evaluate the effectiveness of one product compared to a similar product produced by a different institution or a different process, allowing better choices to be made for continued production. The product produced, released, marketed will be of a higher quality.	**Janet Lathey, Director, Immunology and Assay Validation, Emergent BioSolutions**
Automation and miniaturization will increase in the future	**Eric Halioua, CEO, Promethera Biosciences**
Making smaller manufacturing facilities, fewer and platformed unit operations, and making biopharmaceutical manufacturing more portable and clonable at any part of the world.	**Sourav Kundu, Director, PD, Amgen**
Better controlled commercial manufacturing processes providing more reliable and sustainable delivery of new biopharmaceuticals for the treatment of life-threatening diseases to improve patients' lives.	**Dr. Denny Kraichely, Associate Director and CMC Team Leader, Portfolio Mgmt, Janssen**
Room-temperature downstream processing is here to stay. Single-use technologies will continue to find applications due to their lower capital costs, ease of process turn-around, and lower overall energy requirements.	**Dr. Michel Ultee, CSO, Laureate Biopharmaceutical Services, Inc.**
Disposables will continue to improve and infiltrate the market. They will become cheaper and easier to operate with positive ramifications for the cost of a developmental program, meaning that drug development will become faster and more efficient.	**Dr. John Morrow, Jr., Newport Biotech Consultants**
The higher titers are driving two fundamental changes: To smaller bioreactors and the possible use of 2000L Single Use bioreactors for full scale production, and second transfer of the process bottleneck from upstream to downstream, which is driving a need for improved or new downstream processing technologies.	**Jeffrey C. Johnson, Engineering Director, BioVaccine Process Engineering, Merck**
Over the next 25 years, improved [production] economics will allow for the development of therapeutics and vaccines designed to treat more targeted and specific diseases.	**Michael LaBreck, Global Product Manager, TangenX TFF Products, Novasep**
Big changes are already happening. Now I'm looking forward to the new different, big changes! Which ones? No idea!!!	**Dr. Fausto Vellani, COO, Cerbios-Pharma SA**
Increased product titres and the worldwide adoption of process will lead to price reductions and increased access of [drug] products to the worldwide community. The changes will also lead to a wider range of products being taken forward to clinical trials.	**Tony Hitchcock, Head of Manufacturing Technologies, Cobra Biologics**

Market Trends

Reviewing the past 25 years, it is clear that the biopharmaceutical industry has more than survived the recent economic downturn, and 2012 is looking to be a good year again. This year, our annual survey results show that both biopharma companies and their vendors are spending and investing more in improving R&D and bioprocessing productivity, staff and other infrastructure. A summary of recent trends include:

• **Industry Status is Improving**: The world market for biopharmaceuticals is now about >$145 billion, growing at 15-18% annually. Much of this growth is due to an increasing number and sales of recombinant monoclonal antibodies, now a $45 billion market. New products and new markets, particularly internationally, continue to support market growth, driving more investment in the industry.

• **Industry Spending/Investment is Up**: Survey results indicate that companies are investing more in biopharmaceutical R&D, including hiring staff and expanding manufacturing capacity. Increased spending is occurring in: New technology; Capital equipment; Process development; and Personnel training and development. Vendors are also investing more in product development and new and better technology.

• **Outsourcing Trends Remains But are Slowing**: Outsourcing, including contract manufacture, continues as a major trend, with our data showing 70% of biopharmaceutical companies outsourcing at least some activity. Survey results also indicate the rate of outsourcing is slowing, probably as outsourcing approaches its inherent limits. Companies are taking a much more rational and sophisticated approach to outsourcing, looking at options from a longer-term perspective.

• **Mergers, Acquisitions and Partnering are Becoming More Strategic:** Corporate mergers and acquisitions are being directed to improving R&D pipelines. Many large companies are now focusing more on acquiring smaller companies and licensing-in candidate products.

• **New and Small Company Financing is Tight**: Financing available for new startup and smaller non-public companies continues to be tight, despite an improving environment. Much smaller company financing and expansion is being accomplished through partnerships and collaborations with larger (bio)pharmaceutical companies.

• **China, India and ROW as Biopharmaceutical Manufacturers**: Biopharmaceutical companies in many developing countries serving their domestic, regional or lesser-regulated international markets are experiencing rapid growth, but have yet to pose a threat to U.S. and European dominance of the innovative biopharmaceutical industry, particularly related product development and manufacturing.

• **Pipeline Shrinkage**?: The biopharmaceutical pipeline of products in development appears to no longer be significantly expanding, perhaps due to streamlined or leaner staff and delayed investments in recent years.

• **Single-use/disposable Equipment**: The trend towards adoption of single-use equipment continues, with rapid growth in this market projected. As confirmed by survey data, single-use equipment, particularly for upstream manufacture (e.g., bioreactors), now thoroughly dominates pre-commercial, although fixed stainless steel equipment still dominates commercial-scale manufacturing.

• **Bioprocessing Continues to Improve**: The gradual increase in expression yields continues, with incremental improvements in host cell lines, cell line engineering, expression systems, vectors, promoters, etc. But other improvements are also nearing industry adoption, including large-scale single-use systems and new downstream technologies such as highly-flexible simulated moving bed purification systems. More and better sensors and control equipment are also becoming available, but improvements are needed.

• **Biopharmaceutical R&D Outpacing Drug R&D**: Biopharmaceutical R&D investment is growing, at the expense of drug (chemical substance-based) R&D. It is widely accepted that 40% or more of pharmaceutical industry R&D funding is now going for biopharmaceutical vs. drug development, and this could grow to 50% or more within a matter of years.

• **Downstream is Becoming Less of a Problem**: Survey results indicate that problems are lessening and the industry is finding ways to increase downstream productivity. Downstream processing today remains more of a challenge than upstream.

• **Mammalian Manufacturing is Crowding-out Other Platforms**: More companies, particularly larger ones, are now standardizing their in-house bioprocessing to be solely mammalian based, as higher mammalian cell culture yields and improved technology have made mammalian manufacture more cost-effective and easier than microbial manufacture.

• **Modular Bioprocessing Facilities are Coming**: Multiple bioprocessing equipment and technology developers and vendors are developing modular approaches to bioprocessing. Companies will be able to assemble bioprocessing systems using off-the-shelf or customized modules ready for plug-and-play with other modules (from the same company).

• **Biosimilars are Coming, Finally to the U.S.**: Well over 400 biosimilars and over 350 biobetters are in development targeted for the U.S., EU and other major markets. With private sector insurers expected to rapidly require use of biosimilars wherever possible, the market for biosimilars will likely grow rapidly over the next 5 years.

FDA and Industry are Getting Ready for Biosimilars: In later 2011 FDA finally issued its first installment of biosimilars filings guidance documents, which contained few surprises are unlikely to disrupt ongoing development activities. In many respects, developing a biosimilar is harder than developing an innovative product involving full approval, since it will likely be harder to closely match many aspects of analytical data and clinical and safety.

Cost-containment and Controls: Since most biopharmaceuticals are used for indications for which there are few alternatives, the overall market is rather protected from widespread cost-containment and controls. But in other countries, cost containment and government-directed cost controls continue to adversely affect biopharmaceuticals.

• **Internationalization of Biopharmaceuticals**: Perhaps indicative of a trend, FDA granted the first approval in 2011 for a biopharmaceutical (biologic) manufactured in Latin America. With

the U.S. by far, the largest and most receptive market for biopharmaceuticals, we can expect other companies in developing countries to launch products in the U.S., EU and other major markets.

• **Manufacture in Developing Countries is Increasing**: Biopharmaceutical manufacture outside of the major market countries is increasing, as indicated by BioPlan's Top 1000 Global Biopharmaceutical Facilities Index (www.top1000bio.com), which ranks facilities worldwide in terms of capacity, employment, and production. Lesser-developed countries are seeking to assure domestic manufacture of biopharmaceuticals being sold in their markets. As single-use technologies improve and as modular bioprocessing facilities enter the market, foreign countries will undertake manufacture of needed domestic products.

• **Worldwide Standardization of Manufacturing**: As more biopharmaceutical manufacturing is performed worldwide, companies (particularly large ones) are working to standardize products and manufacturing processes on a worldwide basis. For many, this includes having 2nd- or even 3rd-source facilities actively manufacturing or serving a backups, having received approvals for manufacture for the U.S. and other major markets.

Summary

The past 25 years have seen a maturation of the biopharma industry, and it has transformed from a technology-focused industry, to a process-based, outcomes- and patient-focused segment. Industry participants envision the next 25 years as the time when strategic manufacturing becomes closely aligned with global patient care.

About the Author

About the Author:

Eric S. Langer is president and managing partner at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing firm established in Rockville, MD in 1989. He is editor of numerous studies, including "Biopharmaceutical Technology in China," "Advances in Large-scale Biopharmaceutical Manufacturing", and many other industry reports. elanger@bioplanassociates.com 301-921-5979. www.bioplanassociates.com

Survey Methodology: The 2012 Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 30 countries. The methodology also included 184 direct suppliers of materials, services and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

NOTE: IMPORTANT TO INCLUDE THIS SO READERS UNDERSTAND HOW THE STUDY WAS CONDUCTED

References:

1) 9th Annual Report and Survey of Biopharmaceutical Manufacturing, BioPlan Associates, Inc, April 2012, www.bioplanassociates.com
2) *Top 1000 Global Biopharmaceutical Facilities Index*, BioPlan Associates, at www.top1000bio.com .