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Bioprocessing Outlook 2012: Industry leaders report on the future of bioprocessing

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Q:What are the current trends in Bioprocessing and what challenges/opportunities does 2012 hold?

Dan Klees
Business Development Manager, Life Sciences Industry
Magnetrol International Inc.
Downers Grove, IL

One of the emerging trends that we see is in the area of single-use, disposable processing systems. But, “if you can’t measure it, you can’t control it!”. Magnetrol International is on the leading edge of designing the next generation of disposable, single-use instruments. The future disposable, single-use process measurement instruments from Magnetrol will provide traditional functionality, accuracy, and reliability with the requirements of low cost, and disposability.

Magnetrol is very active in international organizations such as the ASME BPE where the standards are being written for equipment and instrument in conventional biopharmaceutical processing systems as well as disposable, single-use systems. I chair the ASME BPE Subcommittee on Process Instrumentation and the 2012 Standard will have a new part dedicated to process instrumentation. The Standard will be expanded over the next few years to incorporate disposable, single-use, process instrumentation.

Our customers are challenged to manufacture more product of a better first-time quality at less total manufactured cost. To accomplish this, energy usage must be minimized, rework must be eliminated, the process must be optimized, equipment must be scheduled and utilized effectively, product hold times must be minimized, compliance must be assured, and the list goes on.

Magnetrol’s challenge is to help the customer to first measure and then optimize process parameters affecting costs while still assuring safety, purity and efficacy of their intermediate or drug. Our challenge, therefore, is to be involved with our customers at the earliest stages of manufacturing design – and preferably even at the beginning of product development. Reliable, accurate process measurement and control solutions – that optimize yield while minimizing cost – have to be designed with the process; not after the process design!

The opportunities for both the customer and supplier are huge. Value-added partnerships will be solidified – where suppliers take on a role as technical advisors on the customer's team. Our customers expect value-added partners, such as Magnetrol International, to understand their regulatory environment, their processing parameters, and their business model in order to supply measurement solutions that allow the customers to meet their business goals. The days of purchasing "hardware" or "components" are all but gone.

Joshua Froimson
Associate Director of Engineering
Abbott Biologics Manufacturing

The challenge for bioprocessing plants is to select the technologies of greatest value for implementation to match process and future market demands. Abbott employs careful upfront planning for technology selection which optimizes process productivity and compliance, while avoiding future implementation and trouble-shooting issues.

One trend in bioprocessing is the increasing sophistication of instrumentation and controls. This takes the form of more on-line sensors of a wider variety of types, a move of manually collected data from paper forms to control systems entry screens, the increasingly operations-oriented application of process historians and multivariate approaches to process control. All of these take the process in the direction of PAT (process analytical technology), whether a plant is formally adopting PAT or not.

Some of the on-line sensors are on-line variants of analytical instrumentation previously only available off-line (e.g., sensors for measuring viable cell density on-line), while other sensors are entirely new. The shift from paper-based data collection to electronic (but still manual) collection enables plants that have not implemented EBR (electronic batch record) to score some of its advantages, such as automated data validation, real-time alarm generation and plotting of trends using the plant data historian. Output from process historians features increasingly evolved analysis of data, often transcending trend reporting to provide such functionality as multi-batch comparisons and evaluation of processes against defined criteria, e.g., using column chromatography data analysis from actual runs to monitor column health without specific HETP (height equivalent of a theoretical plate) tests. At Abbott we continue to focus on value and production efficiency in every part of our production facility.

Michelle Calhoun
Director of Marketing for Contract Manufacturing Services
Abbott

We continue to see trending towards small scale/high titer products. To address this opportunity, Abbott continues to add to their production capabilities mix as evidenced by the recent installation of two 500L disposables bioreactors. This investment was driven to support Abbott's internal captive use and external contract manufacturing product scale requirements. Careful consideration was made in bioreactor selection to optimize production value in terms of process flexibility and project cycle time requirements. As a leading, long-standing biologics API contract manufacturer with over 25 years of experience, Abbott has seen many trends in production, of which disposables is one that they see continued growth and will continue to support in the future.

Anurag S. Rathore
Professor
Department of Chemical Engineering, Indian Institute of Technology
New Delhi, India

Implementation of Quality by Design for Biotechnology Products: Technical Challenges and Solutions
Quality by Design (QbD) has become quite a buzz word in the pharmaceutical industry in the last 5 years. The regulatory agencies, in particular the US FDA, have spent considerable effort in supporting the rollout via a variety of initiatives such as the QbD Pilot Program. However, a widespread adoption of QbD by the biotech industry is yet to occur.

Challenges that add to the complexity include:

1.The heterogeneous nature of protein products means that complete characterization via analytical tools is not possible
2.Biotech processes are complex and have a large number of process steps and operational parameters that can potentially impact product quality. It is not possible to determine all these effects experimentally.
3.Several of the raw materials used in biotech processes are not well-characterized, thus resulting in process variability.
4.A biotech product has a large number of quality attributes and we have limited understanding on how these attributes impact safety and efficacy of the product.
Opportunities exist via the various initiatives that can alleviate some of these issues:

1.Platforming of biotech processes and analytical methods can make process and product development as well as manufacturing cost efficient.
2.Use of high-throughput approaches for development and characterization of analytical methods and processes can significantly increase productivity and thus result in savings of time and cost.
3.Use of statistical approaches for design of experiments, as well as for multivariate analysis of data, allows us to do more efficient experimentation as well as analyze complex datasets.
4.Use of risk analysis and assessment will allow us to focus on the most critical aspects of process and product development and thus, reduce chances of failure.
In summary, QbD offers a lot of potential with respect to improved robustness and consistency of process performance and product quality. However, a lot needs to be done to get these technical tools and approaches in place to facilitate creation of a QbD approach that is feasible with respect to requirements of time, cost and resources.

Parrish Galliher
Founder and CTO
Xcellerex

For the last 30 years, the biopharmaceutical industry prospered in the “golden age” of generous venture capital, plentiful blockbuster drugs, high margins, and little to no competition. Manufacturing strategy drivers were simply first-to-market, building monster manufacturing facilities, and producing at adequate quality and cost control – “schedule, quality, and cost” in that order.

Today, a sea change in the industry is being propelled by new disruptive drivers: fewer blockbusters, stingy venture capital, smaller niche markets, increasing quality standards, reimbursement pressure, corporate consolidations, and the impending competition of biosimilars. These new trends have intensified the “cost, quality, schedule” struggle, requiring a complete redefinition of manufacturing strategy to survive. As market

sizes shrink and expand into local markets of developing countries, the excess and inflexible capacity of large mega facilities is the wrong capacity for the new future.

In response to these new pressures, manufacturers are transforming their operations and businesses to compete in the new era of globalization: deploying agile, flexible, faster, smaller, better, and cheaper manufacturing capability. The last 5 years have witnessed 10 fold higher titers and the advent of single-use manufacturing technologies. These efforts have yielded many fold improvements in speed, as well as improvements in manufacturing quality, efficiency, and cost reduction.

However, these advances are by no means a panacea and are unlikely to be sufficient alone to guarantee survival in the new era. For example, higher titers have created a new bottleneck in downstream purification with existing technologies, and single-use technologies are even more limited in the downstream space. Further, lack of standardization in the single-use space is slowing industry adoption.

Going forward, new and creative approaches will be required to relieve the cost-quality-schedule struggle. In response, the trends will include:

1.Standardized, agile, flexible, and efficient facilities for “in-market-for-market” manufacturing
2.Standardization of single-use technologies and disposables supply chain security
3.Breakthroughs in productivity and cost of single use upstream and downstream processing
4.Methods and technologies to enable/control of “comparable quality” biosimilar manufacturing
5.Real time in-line PAT analytics for biologics manufacturing; EM, in-process and release testing
6.Technologies that enable faster or real time release of batches of drug substance and product
7.Technologies that maximize efficiency: simultaneous multi-product manufacturing
On the horizon, the next challenge to our industry looms. The advent of very small scale and individualized stem cell and organ therapies will further exacerbate the cost-quality-schedule struggle. Tightening reimbursement limitations and the loss of economies of scale will only fuel the struggle.

In summary, we face daunting but exciting challenges ahead. The new trends in play today are just the leading edge of what will be required to compete in the future.

William Whitford
Senior Marketing Manager
Cell Culture and Bioprocessing
Thermo Fisher Scientific

The industry is witnessing a continued move away from individually sourced process components, to establishing entire systems of materials design that work together in concert. In product development, we are leaving the practice of developing individual clones for a single product. The trend now is to employ a platform approach, establishing an integrated kit of tools including dedicated, well-characterized vectors, a stock of application-ready null-cells and a production media-related selection environment.

In designing unit operations, we see skid-based operations, or assemblies of related components, previously verified through testing to work well in an integrated fashion. In sourcing of materials and equipment we now recognize the value of employing products designed and validated by the manufacturer to work in concert this way.

Thermo Fisher Scientific has the capability to supply platforms of products, employed in closely related unit operations, which have been developed together. For example, powdered SFM culture media was employed in the development of our single-use Powdertainer™ storage systems. Both regulatory and economic value is gained in the material’s closed delivery to our single-use mixers (SUM) for hydration. This hydrated culture medium can then be directly transferred to our single-use bioreactors (SUB) with the capability to collect and

store the harvest in single-use BPCs. These integrated “solutions” provide gains in safety and efficiency in many ways, such as by providing a continuity of raw materials and product contact surfaces. Employing such assemblies of coordinate products is also preparing us for the move into more closed and even continuous manufacturing processes.

Finally, we are seeing a new field of Systems Biology supporting a move from the reductionist mindset of a decade ago, to a more comprehensive “systems” approach. This is driving a stronger focus on knowledge-based approaches to complete manufacturing systems— something our organization is incorporating into our bioproduction solutions.

Juliette Schick, Ph.D.
President
SciLog

Due the vast number of processes involved in the bioprocessing industry, trends seem to manifest themselves in different levels of process development. There are, however, always a few major concepts that transcend processes and applications which share the same fundamental bases-accuracy, sterility and repeatability. Desire for integration of accurate and repeatable single use application systems and sensor technologies is evident in both the Upstream and Downstream processes. At SciLog, we are experiencing an increasing demand for the design of new flexible platforms that are easy to use and easy to validate on a continual basis. In addition to user and process friendly single-use platforms and components, there has also been significant market shift from manual operations to automated processes. In part, automation has been accepted with regard to ensuring data acquisition: an element which comprised a large amount of human interaction and error. Unfortunately, developing acceptance of automation through the chains of organizations has been a challenge until the release of Open Architecture™.

Another challenge that we feel as a market opportunity throughout our industry is the development of industry standards which are refined to a point to ensure business continuity, yet remain flexible enough so they can be applied to multiple applications on the same system. Our responsibility to our end-users is to uphold supply relationships, quality, and bolster them with new standards of operational flexibility to optimize current and future processes. SciLog’s product and development philosophy centers on enabling end users by providing the tools to enhance bioprocessing steps in the early stages to get higher yields and efficiencies. We find it vital to develop partnerships between customers and manufacturers early on to enable long term success through equipment and application knowledge. Today, SciLog’s Open Architecture™ systems allow end users to setup and validate options for bioprocessing in a multi-vendor, multi-application, environment with total control of configurations. This Open Architecture™ offers the bioprocessing market the only platform to fully open scientific and operational constraints previously limited by the business models of other commercial organizations.