Biopharmaceutical Manufacturing Trends 2013

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THE BIOPHARMA industry’s continued focus on process efficiency is being fueled by advances in biosimilars, smaller volume drugs, shorter drug lifecycles (faster trials, development cycles), and high-volume product manufacturing issues.

Biomanufacturers’ Top Trends, 2013

To evaluate the trends that are shaping the bioprocessing segment today, BioPlan Associates recently surveyed 450 global subject matter experts and senior participants on its Biotechnology Industry Council panel of bioprocessing professionals and asked them to identify the most critical factors and trends they expect will need to be addressed over the coming year. While ‘process efficiency’ was a unifying thread, three clear sub-topics emerged: downstream processing; analytical methods development; and single-use system integration. This year, the industry will see an increase in multi-product facilities, selective single-use adoption (both in
clinical and commercial stage), a ramping up of continuous processing, and more advanced automation and monitoring. With downstream processing continuing to lag improvements in upstream, the industry will continue to look for better performing chromatography resins and consider alternatives to protein A.

**DOWNSTREAM PROCESSING**

Downstream purification (separation, filtration and chromatography) continues to be a culprit behind facilities’ capacity constraint problems. It counts as one of the key areas that the biopharmaceutical industry believes must be addressed to avoid short- and long-term capacity constraints, and it is where a large number of industry suppliers and end-users are developing and evaluating new technologies and other options for improving production efficiency.

Biopharmaceutical manufacturing, due to the fact that it operates in a highly regulated environment, tends to be characterized by incremental improvements rather than rapid, major technology shifts associated with other less regulated or consumer-oriented industries. The problem has been that with the significant increases in protein expression levels over the past several years, pressure has shifted squarely to downstream operations, which have not seen the same degree of improvement. This, in return, has resulted in continued bottlenecks in purification and filtration operations. The issues experienced by downstream operators have remained relatively constant over the past few years. And although there are many new technologies under investigation and consideration, few as yet, are being actively implemented.

This year’s trends study revealed 24% of industry participants named downstream processing as the single most critical trend. By contrast, 5% said the same about upstream processing. Within the rather broad area of downstream processing, the research reveals several sub-trends including:

- Process improvements in bioburden control in chromatography columns;
- Development of non-chromatographic recovery unit operations;
- Improving harvest operations through novel technologies;
- Increasing protein concentration in solution, without reducing yield; and
- Purification related to impurity profiles in biosimilars.

There is a general perception that the industry needs better-performing chromatography resins. Results from last
year’s 9th Annual Report and Survey of Biopharmaceutical Manufacturers, in which more than 300 biomanufacturers were surveyed, showed that slightly less than one-third of respondents wanted suppliers to focus efforts on chromatography products, the third-most sought after new product development area of the 21 we identified.

There appears to be some consensus that alternatives to protein A will continue to be sought and developed this year. It is worth noting that while the industry has been clamoring for alternatives to protein A purification for some time, few facilities have made such a switch. For example, last year’s survey revealed 16% of respondents considering alternatives to protein A for existing projects, but less than half that proportion (7%) offer that they will actually be moving away from protein A for existing scale-up or commercial production units over the following 12 months.

In fact, the study found that the long-term trend among facilities interested in protein A alternatives appeared to be decreasing for new production units, while there was modest interest in switching from protein A for existing scale-up and existing production units. In general, though, interest appeared to be waning.

Using protein A chromatography media remains problematic because of the high-cost, limited life of the material and the cost of cleaning/validation. Alternative methods for purification of antibodies have been, and are being developed with longer lifetimes and therefore lower cost per unit of protein produced. However, according to most end-users, protein A “works.” While general interest in alternate purification methods to protein A remain high, actual switching behavior seems to be static or declining.

Still, the environment is ripe for innovative alternatives to emerge, and as long as downstream processing remains in the conversation, alternatives to protein A will be an ongoing topic of discussion.

ANALYTICAL METHODS
In most biomanufacturing segments, it appears that improvements in assays and analytical capabilities are needed or desired. In addition to the continuing needs to assess and document product composition and quality, new demands for assays and analytical capabilities for biosimilars range from proving similarity to determining the unique differences between products. Assays and analytical method improvements are also needed to increase productivity in active agent design, discovery, screening and optimization, as there are too many products continuing to fail very expensively later in development. Most all can agree that it’s preferable to have products fail fast in order to move on to the next, most
promising candidate in the development pipeline.

According to the evaluation study’s results, almost one-quarter (24%) of industry experts tabbed analytical methods development as the top trend of 2013, on par with the percentage citing downstream processing. Common micro-trends within this area included:

• Convenient, high-throughput assays that assess physicochemical properties IgG clones for high level expression and therapeutic efficacy;
• Demonstration of biosimilarity to reduce costs of biologics manufacturing, and analytics to demonstrate equivalent product quality;
• Development of better characterization tools for upstream analysis and optimization; and
• Improved high throughput, high resolution glycosylation analysis.

Clearly, there are multiple addressable dimensions to this topic, and we found a similarly wide net in last year’s Annual Report study where we inquired as to which assay areas most urgently required new or improved testing methods. That is, of the 29 “areas” we identified, 10 were cited as urgent by at least 20% of respondents. These included:
• Bio-assays to assess potency for release of drugs (41%),
• Biophysical characterization during process development (35%),
• Glycosylation (33%),
• Better stability assays (32%), and
• Biotech drug comparability—innovation in this area, ranking it near the top of the list in terms of new product development areas of interest among respondents.

SINGLE-USE SYSTEM INTEGRATION

Although analytical assays rank towards the top of biomanufacturers’ new product development interests, single-use, disposable products are at or near the top of the list. Preliminary data from the study reveals that end-users are interested chiefly in disposable products, bags and connectors (49%), while also expressing a desire for improvements in disposable probes and sensors (30%), disposable bioreactors (29%), and disposable purification (29%). These areas have been consistently in demand for

Disposable devices are making advances and becoming increasingly common in most areas of biopharmaceutical production.
several years now.

Disposable devices continue to make advances in manufacturing and are becoming increasingly common in most areas of biopharmaceutical production. Although, as yet, there are few non-rigid single-use devices (e.g., bioreactor bag liners) used in commercial scale GMP applications, it is likely this will change quickly as new products move through the development pipeline and out of clinical-scale manufacturing. Further, as regulators gain familiarity with the safety profiles and materials used in such devices, necessary approvals for product manufacture are apt to accelerate as well. When this occurs, the market volume for single-use devices is likely to increase significantly.

This year, 22% of the Biotechnology Industry Council members surveyed believed that single-use system integration would be the key trend for the year. Within this burgeoning area, participants identified several sub-trends. These include:

- Building quality into single-use operations to further reduce regulatory activities/oversight;
- Fixing disposable bioreactors that create inconsistent growth due to changes in resins, films, gamma irradiation, and cell line specificity;
- Downstream operations using membrane adsorbers;
- Emergence of flexible and modular biomanufacturing facilities;
- Establishing leachables and extractables guidance for testing;
- Improved upstream contamination investigations from a QA perspective;
- Introducing single-use devices at GMP commercial scale manufacturing; and
- Leachables and extractables [standardization] at clinical and commercial scale.

There are two interwoven trends worth an additional look. The first regards leachables and extractables. Last year, there were reported problems with the reliability and performance of available disposable solutions, with leachables and extractables a key factor. As Rick Johnston, Ph.D., CEO of Bioproduction Group Inc. noted, these issues “undermined confidence in the ability for ... manufacturers to supply material in a timely manner to support production. This led many biomanufacturers to aggressively pursue dual-sourcing and risk-mitigation strategies like holding large inventories, both of which raise overall production costs. It is hoped that in the 2013 time period these issues can be resolved to allow the promise of disposables to be realized in the biomanufacturing setting.”

Indeed, the emergence of flexible and modular facilities, as well as the adop-
tion of single-use devices at GMP commercial scale manufacturing (something already underway) depends in part on resolution of leachables and extractables (L&E) problems. In our 9th Annual Report, we asked respondents to identify the factors that may restrict their use of disposables in biopharmaceutical manufacturing. Fully 7 in 10 (69%) either agreed or strongly agreed that L&E problems were a concern, beating out bag breakage and single-source issues as the most common factor restricting further adoption of disposables. And when respondents were asked about identifying the single most important reason for not increasing their use of disposable technologies, concern regarding L&E headed the list again.

The debate over L&E data continues, but a major concern that end-users struggle with is that the raw material sourcing sometimes is unregulated, putting them at a disadvantage. Because vendors deal directly with raw material providers, end-users feel they are in a better position to test and provide the necessary L&E data as supporting documentation for their products. The desire for this type of data is strongest among scale up/clinical development organizations.
that do not have the resources to conduct such tests in-house. On the other hand, late-stage manufacturing organizations that are in phase III or commercial production are unwilling to take a chance with vendors and would rather generate L&E data themselves to minimize regulatory risks.

If the L&E problem can be addressed, then it is likely that the use of disposables in biomanufacturing will grow more rapidly. While the wheels have been set in motion, the remaining hurdles still need to be cleared. Members of BioPlan Associates expert council believe that the L&E roadblock could be addressed this year.

The trend evaluation study revealed that three topics — downstream processing, analytical methods, and single-use systems — will dominate industry attention, both among end-users and industry suppliers. But it is important to remember that many other trends and themes are certain to shape and influence the market. Product platforms, cost reductions, materials sourcing, supply chain regulatory compliance and biosimilars will all make headlines in one form or another.

When 2013 comes to a close, the industry will be looking to answer three key questions:

1. Where were the breakthroughs in downstream processing innovation to help ease capacity constraints?

2. Did we see significant improvements in assay development that meet the current and emerging industry demands?

3. Was 2013 the year that L&E problems (and related supply chain management issues) were finally put in the rear-view mirror, and a jump in single-use adoption at commercial scale emerged?

Stay tuned for the answers.

References:

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Survey Methodology: The 2013 10th 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 over 300 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 29 countries. The methodology also included over 180 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 United States and Europe.

Beyond Business As Usual: Disrupting the Biopharma Business Model

Panelists Gautam Jaggi, Ernst & Young’s Global Life Sciences Center, Stephen Marc Paul, Weill Cornell Medical College, Tomasz Sablinski, Transparency Life Sciences and Celtic Therapeutics, Bernard Munos, InnoThink and Ben Shapiro, PureTech Ventures discuss how the biopharmaceutical industry must change to meet patient need and assure financial viability.

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Biopharma’s Flexible Imperative

Business forces, bioterror and pandemic risks demand new approaches

By Robert F. Dream, Principal, HDR Company, LLC

RECENTLY, A number of different trends have converged to demand a new type of biopharmaceutical facility, one that emphasizes flexibility and agility. Drawing this new blueprint are:

• business needs to minimize timelines and financial risks;
• “biotech on demand,” and the ability to shore up local manufacturing capacity, quickly, to meet market needs;
• national security needs for systems that can easily and rapidly respond to biological attacks;
• urgent national health needs to protect the public from large-scale, fast moving epidemics and pandemics.

Today’s biopharmaceutical manufacturing facilities are smaller and more flexible, efficient and cost-effective than those of the 1990s, and they are able to adapt quickly to market changes.

The goal isn’t technology in and of itself, but greater product and process know-how for speed to market. With modular
systems, we can now place an entire small-scale clinical production line inside an 18’ x 42’ x 13’ (W x L x H) environment.

Based on defense and health department standards, vaccine manufacturing facilities have been blazing new trails. Traditionally, it has taken between 14 and 20 years to move from pathogen identification to vaccine safety and efficacy trials. The new goal, set by the U.S. Defense Department’s DARPA (Defense Advanced Research Projects Agency), and repeated in specs set by BARDA, is to cover the same ground in less than 22 weeks.

The lifeblood of this flexible, multiproduct and multitechnology future will be the Mobile Bioprocessing Unit (MBU), which has already been built for manufacturing small, clinical-scale quantities of some therapies. (Figures 1-4 illustrate the National Center for Therapeutics Manufacturing, housed at Texas A&M University in College Station, Texas.) The key feature of these mobile units is that they are self-contained, with inherent air handling and other critical equipment and controls built in and standard.

Each MBU is used for a single, biologically distinct technology (bacteria, mammalian cells, plants, etc.), thereby eliminating any cross-contamination issues with regulatory agencies. When they are not being used, MBUs are designed to be moved to cleaning and refurbishing areas, and ready to connect when needed. The goal is to:

- Enable low-cost, rapid production of proteins/products, all of which are correctly folded and biologically active, as well as cGMP-qualified master virus banks and cell lines;
- Draw on extensive clinical use and regulatory history;
- Scale MBUs to large volumes and high
cell densities;
• Feature FDA-qualified cell lines and virus banks;
• Produce cGMP clinical materials affordably and to provide manufacturing and treatment capacity on a moment’s notice.

The Strategic National Stockpile facility for flu vaccine, for instance, calls for 8 to 10 modular process trains for surge production, and allows surge capability to 10 times baseline capacity within 24 hours.

Key features of these facilities will be stockpile pods containing complete process lines, and a lifecycle management program, with scheduled rotation through production.

In addition, DARPA is considering construction of adjacent facilities to integrate and validate “clinic ready” emerging technology platforms. These facilities will be closely integrated with other operations, including animal model development and validation, biomarker evaluation, imaging, GLP pre-clinical studies and animal rule efficacy, and human Phase 1 clinical trials.

VACCINES, BIOTHERAPEUTICS AND PERSONALIZED MEDICINE
DEMAND AGILITY

Business demands are also demanding new facility designs and technologies. By 2016, five of the top 10 biopharmaceuticals are expected to be monoclonal antibodies (MAb’s). Follow-on (biosimilar) versions of these will most likely become available in the coming years due to patent expiry and the introduction of legislation for biosimilars. Personalized therapies will further drive the fractionation of the biopharmaceuticals market, thus increasing the need for smaller batch sizes and campaign-based production schemes.

Business realities, combined with demographic and market forces, will accentuate the national imperative for flexible and more cost-effective manufacturing. Compared with other biopharmaceutical products, monoclonal
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antibodies are large proteins that require relatively high doses—and traditionally necessitate high-volume manufacturing process equipments/systems and facilities. Many biopharmaceutical facilities are still designed as traditional fixed equipment/systems and facilities, with fixed piping and vessel layout and large bioreactor volumes. Such facilities require a significant financial investment along with high total installation costs.

Recent increases in cell culture yields/titer have led to significantly reduced bioreactor volume requirements, which again have opened the door for single-use manufacturing technologies such as pre-sterilized assemblies of single-use bags, tubing and filters that are only used once and then disposed of. With a financial investment reduction and simplified installation, single-use technology could be more appealing than other fixed technologies.

Combining single-use technology and high-yield processes could further reduce the price tag for comparable facilities by 50 percent. This combination is being pursued in a number of biopharmaceutical facilities today—the full effect is truly a paradigm shift.

Additionally, single-use technology runs a much lower risk of batch-to-batch contamination, which is of particular importance in multipurpose facilities. A facility based on single-use technology is
easy to reconfigure and can therefore be ready for a new product in a matter of days. This flexibility translates to reduced development timelines and thus accelerated time-to-market peak.

In an increasingly fractionated market, the need for speed to secure market shares is more important than initial minimal cost of manufacturing. And with remarkably increased cell titer, the cost contribution from the manufacturing facility is limited compared with development costs.

With single-use technology, it becomes possible to optimize facility installations based on anticipated product lifecycle stages. For instance, to start with, the strategy could be to use just one single-use bioreactor to get material for clinical trials and then upgrade the facility with additional bioreactors later in anticipation of market supply production while clinical trials are taking place. As the next pipeline product must be developed, the facility can change the lifecycle stage back to clinical production and the extra bioreactors moved to a market supply expansion facility. Such a strategy becomes possible because single-use technology is so decoupled from the facility building itself.

As an interesting side effect, environmental impact studies show that single-use...
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technology is up to 50% less energy-intensive than fixed reusable manufacturing. It may appear counterintuitive, but the emissions from disposing single-use material are more than offset by elimination of the cleaning and sterilization processes required for reusable technology, basically because heating up many tons of water and metal is extremely energy-intensive. Full implementation of high-yield processes and single-use technology results in facilities with a markedly reduced carbon footprint per kilogram of product compared to the fixed facilities of the 1990s. Usually 60% of piping in a fixed facility is installed to perform CIP/SIP.

The need for local biopharma manufacturing capacity is increasing in the fast-growing emerging markets as the customer base expands and national initiatives manage the markets. The trend is being amplified by blockbuster patent expiry and the implementation of regulatory legislation for accelerated pathways for biosimilars. For biopharmaceuticals, emerging markets are not about low-cost manufacturing hubs, but about being on location to get access to the local market. Consequently, many big pharmaceutical companies as well as local manufacturers are investing in new facilities in these countries. A blueprint facility concept that can be established as interesting markets develop will become an important strategic asset for biopharmaceutical players with global aspirations.

In reality, the important issue is not stainless steel or single-use technology, but rather how technologies could be combined to provide the most productive and cost-effective process in a fast and predictable way. Choosing one or the other technology concept or a hybrid of the two depends on both strategic considerations and feasibility studies of each individual case.

Clearly, biopharmaceutical manufacturing’s paradigm is changing from stainless steel to hybrid combinations of single-use and stainless steel, and complete single-use facilities. Manufacturers are already exploring opportunities, aggressively, and we can expect this trend to continue.
IN BIOPHARMACEUTICAL manufacturing today, quality management is critical for steering clear of production problems, capacity bottlenecks, and operation failures. The good news is that manufacturers appear to be doing a better job over the past 10 years.

In our “9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production”, we evaluated, along with more than 80 other biomanufacturing trends, the frequency of batch failures among global biomanufacturers. We weighted information shared by 302 respondents to estimate the batch failure rate for the industry. Based on the responses, batch failures occur on average every 60.3 weeks per facility. This is a significant improvement over last year’s average of 54.5 weeks, and shows a continuing trend over the past five years (Figure 1). Indeed, in 2008, we found batch failures to occur every 40.6 weeks. This means that in five years, the batch failure rate has improved by 49%.

Delving further into the responses, we find some interesting patterns in play. For example, the proportion of respondents who said that the last batch failure at their facility occurred either two years or more ago stands at 36.5% this year, up significantly from 29.9% last year, 25.8% in 2010, and 26.7% in 2009. On a similarly encouraging note, the proportion experiencing a failure in the past one to three months dropped to 14.1% this year.
after being steadily around the 20% mark for the past few years (18.5% last year, 21.1% in 2010, and 21.6% in 2011.)

Tempering the good news, though, is our finding that the proportion of respondents experiencing batch failures very recently (within the last week or last month) is markedly up. This year, more than 1 in 10 (10.6%) reported a failure either within the last month (8.2%) or the last week (2.4%). This is a step above the 7-8% who have indicated this in past studies.

Taken together, though, the news on the whole is encouraging. The continuing reduction in frequency of batch failures is a good sign, and represents a maturation in performance, likely even within smaller organizations. Some of this improvement is directly related to training of operations staff, which, according to the study, received significant budget increases this year.

Although the specific causes contributing to this improvement are not fully defined, companies are clearly managing their manufacturing more effectively, most likely by: improving their process design; resolving supply chain issues; using increased process monitoring and process analytical technology (PAT); gaining experience in preventing contamination; and otherwise learning from prior contamination episodes. Also, it is possible that “natural selection” is at work, with those companies experiencing more process failures also tending to have other problems contributing to failures.

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 29 countries. The methodology also included 185 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.
One potential reason for the decline in batch failure frequency is the industry’s increased adoption of PAT. In many respects PAT is nothing new and involves no new specific requirements beyond those needed to support cGMP approval. PAT, Quality by Design (QbD) and other process measurement-based quality programs are efforts to better quantify, model and otherwise understand manufacturing processes.

Our study shows that continued improvements in sensors, probes and analytical equipment are facilitating process quantification and PAT. Thus, as bioprocessing becomes increasingly monitored by improved and new chemical, physical and microbiological detection methods and assays, including single-use sensors/probes, the resulting data will increasingly support and be used for mathematical modeling and risk analysis. Besides this technological progress promoting increased use of PAT or comparable quality programs, industry adoption will also likely increase as PAT is recognized as an effective method to increase productivity by reducing waste, improving yields, increasing automation and facilitating other cost-saving measures.

Our survey data supports this view. When we asked respondents about the quality initiatives they have implemented, just 21.3% cited PAT, the lowest of the 12 initiatives we identified, and far behind others such as QbD and risk analysis. This may not be surprising, given that adoption of PAT is voluntary. However, when we factor in respondents’ plans for the next 12 months, the story changes. Indeed, 29.3% of respondents plan to use PAT in the next year, the highest proportion of any of the initiatives, and up from 16.1% who responded that way last year. This puts PAT adoption on par with process modeling (52% using or planning) and knowledge management (50.6%), and ahead of other initiatives such as multivariate data analysis, factorial test-
ing of critical process parameters, and stage gate and in-line product reviews.

Increased use of PAT may also be owing to the lessening burden presented by various hurdles to implementation. When we asked respondents about the most significant hurdles in implementing PAT, we found that, in general, most factors are on a multi-year decline. For example, the most common factor identified as significant or very significant, “time required to implement,” was cited this year by just under three-quarters of respondents, down from 79.5% in 2009.

REGULATORY REQUIREMENTS MORE OF A VENDOR PROBLEM
Regulatory issues remain a concern for PAT adoption, and they’re also a key problem when looking at quality control in supply chain management. With PAT adoption increasing, and the frequency of batch failures decreasing, we examined what quality problems can be traced to vendors. In keeping with the positive findings from above, we find that overall, vendor problems are declining.

In fact, the only area in which significantly more respondents this year saw a problem was in vendors’ inexperience with industry’s regulatory requirements. This year, this problem was noted by 31.3% of our respondents, up from 28.1% last year, and halting a 4-year downward trend. This may reflect an increased view of the importance of regulatory factors and the perception and need to understand requirements.

Vendors are taking note of this issue, too. When we asked 185 suppliers to tell us the areas in which they perceive their clients are demanding additional support, 30.5% indicated better regulatory compliance, ranking this area higher than others such as lower prices (29.3%), better quality product offerings and better IP protection.

On the whole, though, most of the other quality issues traced to vendors by biomanufacturers have declined in importance. This year, as they did last year, respondents indicated that the key problem from vendors involves making promises they cannot keep (41.3%). (See Figure 2.) Even so, the proportion citing this has fallen relatively significantly from last year, when it stood at 49.1%. Other problems that have seen significant drops include poor quality of products (just 27.5% this year, as compared to 45.6% last year and a 5-year high of 53.8% in 2010), and poor quality of service (26.3% this year compared to 34.2% last year and a 5-year high of 45.8% in 2009).

GLOBAL QUALITY SUPPLY MANAGEMENT
The declining significance of problems
traced to vendors might be a reflection of increased auditing that manufacturers are undertaking in the supply chain. We separately asked respondents to identify what, in the past 12 months, their organization has done to assure consistent quality in raw materials and ingredient supply. We found that a majority (51.4%) audited their suppliers more frequently, a relatively significant jump from 45.2% last year who were more frequently auditing suppliers. The proportion of respondents implementing more dual-sourcing also increased, from 39.4% last year to 45.9% this year.

Some factors dropped on a year-over-year basis. For example, the proportion of respondents who said that they audited secondary suppliers (those supplying their suppliers) fell from 49% to 40.5%, while this year only 36.5% implemented more comprehensive audits, down from 45.2% last year.

Even so, on a number of counts, we found that biomanufacturers are adopting more comprehensive quality supply management: More have developed new, more rigorous tests for incoming raw materials and supplies, while almost one-quarter have increased the volume of testing of
incoming raw materials and supplies.

Comparing responses from biotherapeutic developers and CMOs yields some interesting divergences. CMOs, at a rate dramatically higher than biomanufacturers, are auditing their suppliers more frequently and implementing more dual-sourcing. They are also more likely to be verifying vendors’ certificates of analysis, and specifically identifying secondary suppliers.

By contrast, biomanufacturers appear to be much more active than CMOs in demanding that their suppliers demonstrate higher levels of GMP/GLP compliance, implementing more comprehensive audits, verifying the origin of individual ingredients more carefully and holding more frequent meetings with vendors.

We find a divergence in actions on a geographic basis, too. U.S. respondents are for the most part more active than their Western European counterparts in quality supply management. Some of the larger disparities we found were in: Implementing more dual-sourcing (61.1% of U.S. biomanufacturers vs. 36% of Western European respondents); and Auditing more suppliers, including secondary suppliers (52.8% U.S. vs. 28% W. Europe).

**OPTIMISTIC PICTURE**

All told, our data paints a fairly optimistic picture. The frequency of batch failures is down to the lowest point in five years, and biomanufacturers are stepping up their supply chain quality control while complaining less of problems that can be traced to those vendors.

Despite its promise, PAT implementation remains slow and uneven, leading some to ask when this initiative will achieve its promise. Our data signals that perhaps the industry is finally ready to move to mainstream adoption of PAT. While intentions to implement may have outstripped reality in previous years, with improving economic situations and increased budgets, this may be changing. The success of PAT and QbD applications in pharmaceuticals will depend on better analytics, allowing biomanufacturers to make a strong business case for using these tools.

**References**


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