**Pharmaceutical Manufacturing**
**Topic: Manufacturing Quality Control**
**Pub Date: June 2012**
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**BioManufacturers Reporting Fewer Batch Failures:**
***PAT Adoption Increases; Fewer Problems Traced to Vendors***

In today's biopharmaceutical manufacturing environment, quality management is critical for steering clear of production problems, avoiding 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* [1], we evaluated, along with more than 80 other biomanufacturing trends, the frequency of batch failures among global biomanufacturers. This year, the 302 respondents indicated frequency of batch failures, which we weighted to estimate the batch failure rate for the industry. Based on the responses, average batch failures occur every 60.3 weeks per facility. This is a significant improvement from 54.5 weeks last year, and shows a continuing trend over the past 5 years. Indeed, in 2008, when we measured the batch failure rate, we found it to occur every 40.6 weeks. This means that in 5 years, the batch failure rate has improved by 49%.

**Fig. 1: Batch Failures, Average Weeks per Failure, per Facility, 2008-2012**

| | Batch Failure, Avg. Weeks/Failure |
|---|---|
| 2012 | 60.3 weeks/failure/facility |
| 2011 | 54.5 weeks/failure/facility |
| 2010 | 50.9 weeks/failure |
| 2009 | 51.1 weeks/failure |
| 2008 | 40.6 weeks/failure |

*Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2012, BioPlan Associates, Inc.*
*www.bioplanassociates.com*

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 2 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 1-3 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 quality and management problems contributing to failures.

**PAT Adoption on the Rise**

One potential reason for the decline in batch failure frequency is the industry's increased adoption of Process Analytical Technology (PAT). PAT is defined by FDA as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." 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 of PAT 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 currently 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 testing 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 nearly three-quarters of respondents, down from 79.5% in 2009. And while "insufficient people in-house to manage implementation" remains an issue, it also continues a gradual decline.

This year, worries over cost of implementation appear to have leveled off or declined. This could mean that budget concerns are being resolved. Alternatively, PAT users and others may be recognizing the benefits that PAT can provide. The proportion identifying regulatory issues as hindrances - such as uncertainty over how regulators will deal with information generated by PAT, or that implementing PAT will increase the risk of regulatory evaluations due to small infractions or excursions – appears to be relatively steady.

**Regulatory Requirements More of a Vendor Problem**

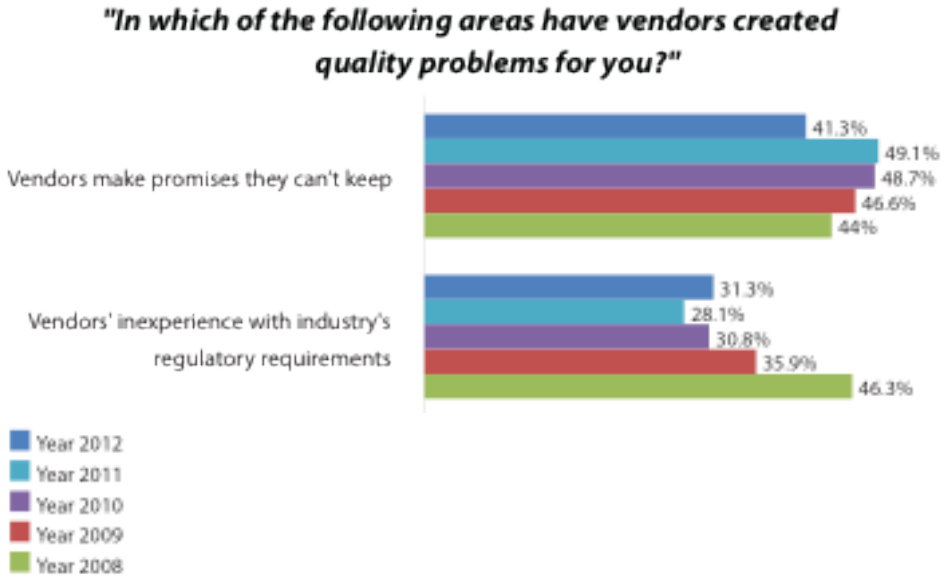
Regulatory issues remain a concern for PAT adoption, and they're also a key problem when looking at quality control in supply chain management. With PAT adoption increasing, and the frequency of batch failures decreasing, we examined what quality problems can be traced to vendors. In keeping with the 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. (The percentage of respondents complaining that vendors have not filed Device Master File on their product also increased, but only marginally, from 13.2% to 13.8%.)

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.

Aside from vendor issues with regulatory requirements, 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%). Even so, the proportion citing this has fallen relatively significantly from last year, when it stood at 49.3%. 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).

**Fig. 2: Selected Quality Problems Traced to Vendors, 2008-2012**




*Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2012, BioPlan Associates, Inc.*
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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. US 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 US biomanufacturers vs. 36% of Western European respondents); and Auditing more suppliers, including secondary suppliers (52.8% US vs. 28% W. Europe);

The only two areas in which Western European respondents appeared significantly more active than US respondents were in auditing suppliers more frequently and testing individual ingredients.

**In Conclusion**

All told, our data paints a fairly optimistic picture. The frequency of batch failures is down to the lowest point in 5 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, it has been close to a decade since the FDA's landmark guidance on PAT, and 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 year, with improving economic situations and increased budgets, this may change. 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 to maximize yields and minimize quality defects.

References:

1. 9th Annual *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: A Survey of Biotherapeutic Developers and Contract Manufacturing Organizations*, BioPlan Associates. www.bioplanassociates.com

## About the Author:

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**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.

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