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Biopharma Manufacturing Trends 2018

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Downstream Gears Up

Modern biopharma is cautiously melding new downstream technology into their processes

By Eric Langer, President/Managing Partner, BioPlan Associates

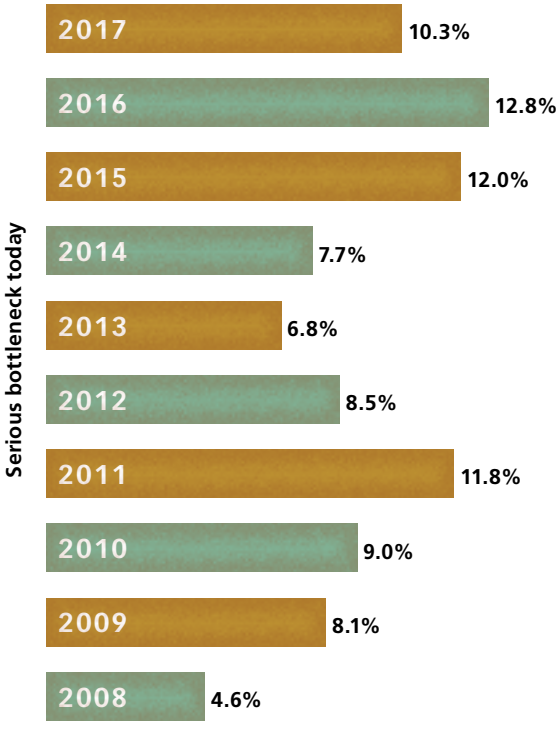
Downstream processing continues to present problems for the biopharmaceutical industry in terms of limiting capacity. To address these problems, industry suppliers are actively developing new technologies to improve downstream processing. And bioprocessing facilities continue to seek out and evaluate these technologies. In our 14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production,[1] we assessed the current downstream processing situation by asking 227 industry end-users and 131 suppliers where they see the future trends.

Adoption of new downstream technologies and their ability to head off near-future capacity constraints have a clear impact on biopharmaceutical manufacturing. Growth

Exhibit 1

Impact of Downstream Processing on Overall Capacity, 2008-2017

"At my facility, downstream processing is impacting capacity and overall production as follows:"



in the industry has hovered around 12-15 percent annually for well over a decade, and industry capacity has to keep up with that demand. Further improvements in upstream productivity are also creating bottlenecks downstream. But bringing on new technologies can be tricky in this highly regulated industry. Regulating bodies like the FDA and EMA must assess the impact on quality and safety related to production changes, which slows adoption of new technologies, even as the industry need for improvement mounts.

In recent years, upstream processing technologies have made fairly significant advances to help increase capacity and remove bottlenecks in the biomanufacturing system. Partially because of this, the onus is now on expanding downstream processing technologies.

Exhibit 2

Selected New Downstream Processing Solutions

Downstream Purification (DSP) technologies being considered in 2017

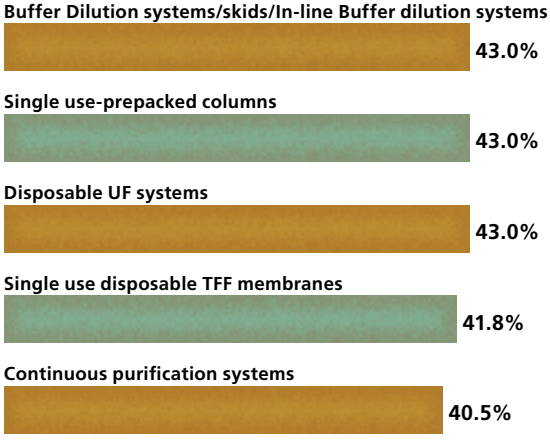


Table 1

DOWNSTREAM OPERATIONS CAUSING GREATEST PROBLEMS	PERCENT
Affinity resins/Protein A/Capture Steps	14.3%
Virus filtration	9.5%
Buffers, large volumes	7.1%
Harvesting step	7.1%
Continuous Bioprocessing (move from Batch)	7.1%
Column packing	4.8%

In this year's study, industry respondents reported that downstream processing was continuing to impact their capacity. This year, 50 percent of respondents to BioPlan's survey said they were experiencing at least "some bottleneck problems," compared to 45.7 percent last year. Although not as severe as downstream processing problems have been in the past, clearly this operation area continues to create capacity issues for a large number of biopharmaceutical manufacturers. For example, 10.3 percent indicated this year that they were experiencing "serious bottlenecks today."

NEW TECHNOLOGIES ON THE WAY

Despite the need for new technologies, their adoption is sluggish. This is due in part to incremental improvements like streamlining existing processes and elimination of purification steps that reduce the sense of urgency for adopting new technologies. But much of the concern for adopting new technologies stems from the regulatory factors like the need to test novel devices, evaluate new product contact materials, and to address regulators' concerns. At

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present, the most commonly evaluated DSP technologies are buffer dilution systems and single-use prepacked columns (both currently being considered by 43 percent of respondents).

Other new downstream processing technologies are also being evaluated, including:

- Membrane technology
- Single use filters
- High capacity resins
- Filters instead of resin chromatography
- Alternatives to chromatography
- Centrifugation
- On-line analytical and control devices
- Countercurrent chromatography
- Precipitation
- 2-phase systems
- Moving beds
- Synthetic biology, enzymatic transformations, etc.
- Field fractionation
- Small substrates

SPECIFIC AREAS OF CONCERN

Our annual report also identified specific problem areas in downstream processing. The primary bottlenecks appear to be related to efficiency, yield and quality of downstream process flows, particularly in harvest and chromatography steps. However, there was a wide variety of responses to unit operations and downstream areas causing concern. This suggests that there is unlikely to be a single technology that can solve all downstream processing woes. Some of the biggest problem areas are listed in Table 1.

Other areas of concern included leachates and extractables for single use devices, need for better monitoring and sensors, measuring protein concentration, facility logistics and integrating Process Analytics Technology (PAT).

Chromatography problems are typically associated with resins. Industry experts told BioPlan there are too many available, they're too similar, and they don't have enough differentiating features. They are hoping to see technological solutions; new affinity formats, ligands, chemistries and resins; new Protein L/mAb fragment resins; more and less expensive custom ligands; and protein A alternatives. End-users want more Protein L and other resins for modified antibody purification, and these may be well-suited for isolation of abbreviated and other smaller engineered versions of monoclonal antibodies.

Another area in need of improvement is membrane chromatography. Membrane capacity is the biggest problem here, then limited functionalities and choices among membranes, and limited single-use options were the next major concerns. Industry experts suggested multi-layered, mixed-mode membranes, more diversity of membranes and more variety of beads, ligand, linkages, resins and formats. They

also wanted more choices in binding-and-elute/capture membranes, particularly for Protein A.

Column packing creates issues because it is too time-consuming, unpredictable, inconsistent, and costs are too high. Industry experts indicated they would like to be able to use custom pre-packed columns. They also wanted column packing automation and resins that are more packing friendly (rigid).

Lastly, issues arising from clarification/harvesting operations include fouling, complexity/too much variety, and scaling and selection problems. New technologies industry insiders would like to see include flocculation and the ability to painlessly scale up and down their bioprocessing. In addition, development of processes at small and large scales so that the same process is predictable at different scales was also desired.

WHERE THE INDUSTRY HAS MADE IMPROVEMENTS IN DOWNSTREAM PROCESSING

Downstream processing constraints have caused bottlenecks for a number of years. Some continue to be evaluated and implemented. In our study, we asked respondents what actions their facilities have invested in for improvement of downstream processing issues. Top response was: Cycled columns more frequently (39.3 percent of respondents). Other responses that were above 35 percent included, "used or evaluated alternative ion exchange technologies," "investigated single-use disposable downstream technologies," and "used or evaluated membrane-based filtration technologies."

Interestingly, there are significant differences in which technologies are being implemented between biomanufacturers and CMOs. Over 50 percent of CMOs reported that they investigated single-use disposable downstream technologies (53.8 percent), while only 33.8 percent of developers reported the same activity. Likewise, 53.8 percent of CMOs reported that they used or evaluated membrane-based filtration technologies vs. 32.4 percent of developers.

There were also differences in CMOs and developers in what technologies they were considering adopting. CMOs showed the greatest interest in single use prepacked columns (72.7 vs 38.2 percent of developers), single use disposable TFF membranes (63.6 vs. 38.2 percent of developers), continuous purification systems (63.6 vs. 36.8 percent of developers) and single use filters (54.5 vs. 33.8 percent of developers).

These differences are likely explained by the fact that CMOs are incentivized to adopt new technologies because their needs are more immediate. In addition, they are motivated by cost-savings and the associated need to develop standardized manufacturing platforms. They can also pass related costs

on to their clients. And by their nature, CMOs must be able to handle a more diverse and larger number of processes and products. These attributes suggest that CMOs will continue to lead the way in adoption of new downstream technologies to alleviate their bottleneck problems.

BROAD OPPORTUNITIES FOR NEW AND IMPROVED PRODUCTS

In analyzing the annual data, it is clear the bioprocessing community is actively looking for new and better technologies. However, due to the highly regulated nature of the industry, these technologies may require a long implementation period, during which time only incremental changes may be made. Indeed, incremental changes are more the norm than broad sweeping technological revolutions.

The conservative nature of the industry in adopting new technologies is well-founded. Some of the issues include safety/regulations, concerns about capital and operating costs, desires to avoid overly complex technologies, extensive training of staff and changes involve shifting widespread dedication to established technology. Current technologies are, in some cases, decades old. And they work, without causing public health issues. Therefore, a natural avoidance of investing in new technologies has been present in the industry for years.

These issues can be overcome once proof that regulators are on board with new technology is available, and once operating staff are comfortable with new protocols.

REFERENCES

1. *14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc. April 2017, www.bioplanassociates.com*

SURVEY METHODOLOGY

THE 2017 14TH ANNUAL REPORT AND SURVEY of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 227 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 25 countries. The methodology also included more than 131 direct suppliers of materials, services and equipment to this industry. This year's study 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.

Biopharma Benchmarking Unveils Performance Variance

Performance gaps suggest that it's time for biopharma manufacturing companies to focus on operational excellence

By David Keeling, Ralf Otto, and Alberto Santagostino, McKinsey & Company

The complexity of biopharmaceutical manufacturing has made operational excellence a relatively low priority to date, with manufacturers focused primarily on delivering an adequate supply of quality product. As the industry grows and evolves, however, the focus on operational excellence is increasing, and manufacturers are beginning to look at their peers to understand best practices and their own performance potential. As they do, McKinsey's proprietary Pharma Operations Benchmarking service (POBOS Biologics) reveals notable performance variations among biomanufacturing sites, reflecting the immaturity of these operations. These performance gaps suggest that biomanufacturing companies should take a good look at the way they run their operations and consider whether it is, indeed, time to step up.

CHALLENGED BY THE BASICS

Biopharmaceutical manufacturers have dealt for some time with their products' complex and unstable production processes and relatively low yields. Securing product delivery at sufficient quality has historically been considered challenging enough, therefore, without taking the risk of pursuing production improvements or a transfer to better facilities. Not surprisingly, it is accepted in the industry that variation in output, yields, productivity and quality is simply inherent to biopharma manufacturing. Operations are run at different levels of effectiveness (for example, costs, labor productivity and capital productivity), with technical performance varying as well. As a result, management's focus in biomanufacturing to date has — justifiably — been on

supplying the market, rather than improving established operations.

NO LONGER A DIVERSION

Today, the landscape of the industry is changing. Biosimilars are becoming a reality, making it more difficult to command significant price premiums for biopharmaceuticals, particularly in areas in which innovation may become more difficult, such as in inflammation treatments. Yet the biopharma industry is still more profitable than traditional pharma and has grown steadily for a number of years. In fact, the share of cost of goods (COGS) sold attributable to biomanufacturing in Big Pharma is increasing steadily. Where biomanufacturing was once a minor diversion for pharma's technical-operations organizations — generating a limited share of total costs — many Big Pharma players today have, or aspire to have, a substantial part of their operations in biopharmaceuticals. Simultaneously, biomanufacturing is becoming increasingly industrialized, moving steadily from the frontiers of science into a new manufacturing mainstream.

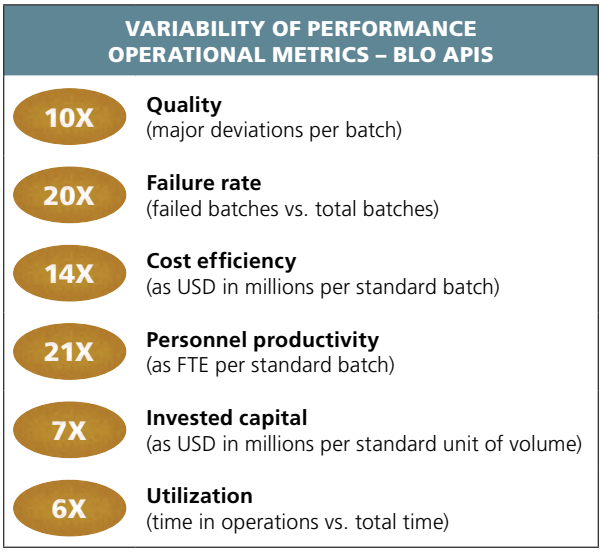
WHAT IS EXCELLENCE?

As the industry changes, executives in biomanufacturing debate the potential for true performance improvement in their operations. Their expectations range from quality improvements and multiproduct flexibility to faster cycle times or throughput and an enhanced cost position. As they pursue these enhancements, they look to understand the true potential of their manufacturing sites, addressing a broad set of performance dimensions — such as process robustness, capacity utilization and lead time — that are as important as, or more important than, productivity itself.

As a result, there is already a strong sense that the industry is moving in the right direction, with some players beginning to take steps to achieve both technical and operational excellence. These players are following a path similar to the one taken several decades ago by a number of chemical active pharmaceutical ingredient (API) manufacturers, moving one step at a time toward more effective operations. Some even find themselves ahead of the curve, having built, or begun to build,

Exhibit 1

Variability of performance operational metrics for biopharmaceutical APIs



operational and technical expertise that puts them at the forefront of the biopharma industry. They are operating multiproduct facilities at a high level of utilization, have rapid batch and product changeovers, and are seeing excellent cost, quality and delivery results.

It is generally understood that certain players perform better than others, but those who have tried to understand their performance vis-à-vis that of the industry have found little transparency, making it difficult to compare the results at different sites or discover the industry's true level of competitiveness. Understandably, many manufacturers are asking themselves important questions:

- Which performance metrics should we consider?
- What does good performance look like?
- How big is our opportunity for improvement?
- Are there any trade-offs? For instance, does increased productivity hinder quality?

BENCHMARKING PERFORMANCE

To uncover the true potential of a given biomanufacturing site, it is essential to ask the right questions, look at the right performance indicators, and make the right comparisons. Companies should begin by attempting to benchmark themselves against their industry peers, assessing the performance of each biomanufacturing site across the board, whether at the site, line or product level. Where available, a stringent benchmarking exercise will provide insights into important factors such as:

- Technical performance in relation to indicators such as yield, titer, success rates and improvement rates
- Operational performance characteristics such as utilization and cycle times
- Productivity factors such as costs, labor, capital and inventory
- Quality considerations such as the level of regulatory scrutiny, deviation rates and CAPA rates
- Structural factors such as capacity, technologies, automation levels, location and salary structure
- Complexity related to batch record entries, critical process parameters (CPPs), number of products and frequency of product transfers
- Organizational health indicators such as education levels, health and safety, turnover and labor allocation

McKinsey's global POBOS Biologics benchmarking has been used to assess these aspects across several biomanufacturing sites. This tool, which covers a big part of today's global biomanufacturing network (including originators, emerging biosimilar players and CMOs) across various locations, provides a view into the reality of the biomanufacturing industry, perhaps for the first time.

Companies should begin by understanding the structural factors that define the maximum threshold of production performance.

One finding is the surprising variability in performance in the industry across all parameters (Exhibit 1). Even in the more standard fermentation of monoclonal antibodies, the cost per standardized batch for some players is significantly greater than $1 million, whereas for others we have recorded significantly lower costs, even below $400,000 per standard batch. For the latter manufacturers, the COGS of the biopharmaceutical API (at less than $1 per dose) is so low as to be comparable to, or even negligible relative to the COGS required to fill and finish the drug product in a prefilled syringe (about $1.30 per unit).

Another important finding is that there is no real trade-off among the various performance dimensions. Players that do well in one category tend to do so across the board, from quality to cost and from lead time to success rate. In most cases, the gap between high and low performers depends on how well the operations are run, rather than on structural factors or complexity. In fact, there is no clear correlation between complexity — including such factors as the number of products, the number of product transfers and the number of regulatory agency registrations — and performance.

The impression from the field is that the competence and experience of each site drives most of the differences in performance. For example, several complex multiproduct sites — both top 20 pharma companies and CMOs — were doing more than tenfold better than a group of single-product sites, because the latter were relatively inflexible and conservative in their way of running operations.

However, there is also evidence that adding complexity does not help a site that is still relatively new and lacks the appropriate competencies. In one case, the transfer of an additional product to a site with below-standard competencies triggered a series of compliance problems, causing batch failures and significant delays in the manufacturing schedule.

Finally, it appears that high performers adopt new technologies to the greatest extent possible within the structural constraints of their manufacturing site, such as the addition of disposables in the upstream seeding processes. These high performers are not afraid to undertake the complications inherent to change controls or regulatory submissions when doing so will bring about performance improvements. Looking more closely, there may be even further interesting differences in the industry's approach to day-to-day operations, including regulatory strategy, plant utilization practices and the approach to operational excellence.

DIFFERENCES RUN DEEP

Looking more closely, there may be even further interesting differences in the industry's approach to day-to-day operations, including regulatory strategy, plant utilization practices, and the approach to operational excellence.

Regulatory Strategy

In looking at the number of entries in a batch record, some players add complexity beyond the point of increasing control, whereas others have gaps in their regulatory strategy. In fact, we observe a variance of 3x among the various players. This difference in approach is confirmed by the fact that the complexity of the batch records strongly correlates with the number of CPPs in play, suggesting that players that adopt a stringent regulatory strategy in one area tend to do so across the board. (The observed variance for CPPs is even more marked, at 10x.)

Most interestingly, the approach to regulatory strategy also correlates closely with the site's quality performance, albeit up to a threshold, indicating that specifications that are too simple may engender less-compliant operations. Above a certain threshold, however, tighter control no longer makes a positive contribution.

Plant Utilization

The majority of the plants assessed to date appears to be vastly underutilized, with upstream time in operations normally ranging from 10 to 40 percent (on a 24-7 schedule). Both structural factors and managerial mindsets are behind this arguably limited performance.

Mono versus Multi: Many sites have been built either as monoproduct sites or with lines dedicated to a single product. This creates a challenge for the manufacturer, because one product may not be enough to utilize a site's full capacity, but two products may be too much. Given the high value of biopharmaceuticals, we find that COOs typically prefer to err on the side of excess capacity, allowing a site to be inefficient rather than risking a shortfall in the drug supply if market forecasts are inaccurate.

In contrast, in facilities that are engineered from the beginning as multiproduct facilities, with the capacity and flexibility to handle a number of products, the variability of product-demand forecasting begins to balance out statistically, posing less of a challenge to product delivery as utilization rates increase.

Capacity management: Looking at site utilization, most sites have uptime of 20 to 40 percent of available time, and net production time of 10 to 25 percent. Further, 20 to 30 percent of available time is spent on nonproduction activities and other losses, often leaving idle time of as much as 40 to 50 percent. We believe there is room to optimize nonproductive time. Net production time is small compared with what the pharmaceutical industry is used to achieving in the manufacture of small-molecule APIs, i.e., 50 to 60 percent, because the nonproduction activities inherent to the equipment batch cycle are extensive and, in addition, there is a significant share of time that goes into maintenance activities and avoidable losses. Further, we have observed a few players that have already managed to operate their assets more effectively, reducing the amount of nonproductive time by using a mix of operational-excellence initiatives and adopting technical solutions such as disposable equipment.

The uncertainty, variability and performance issues that have characterized biomanufacturing operations in the past have underpinned the choice to build in high idle-time buffers to protect supply. Such a choice is surely savvy in most circumstances, given that most biopharmaceuticals have market values that do not justify any risk of a supply shortage. Nonetheless, the same players that have managed to gain better control of their nonproduction time and are running more effective operations do generally operate with higher utilization rates and a smaller idle-time buffer, without incurring any significant issue. A focus on performance excellence allows these sites to address many of the losses, failure rates, changeover times, breakdowns and lengthy preventive maintenance that are the main drivers of uncertainty.

Approach to Operational Excellence

Instituting operational excellence improves performance across the board; in fact, improving performance along one dimension brings improvement along other dimensions. For example, excellence in operations delivers improvements in quality as well as improving cost performance. We have observed that quality correlates strongly with costs, with an R2 of greater than 0.6. The rule of thumb is that the "major deviation per standard batch" key performance indicator (KPI) correlates with the "cost per standard batch" KPI, because each 0.1 increase in the incidence of major deviations per standard batch is linked to

Biomanufacturing is becoming increasingly industrialized, moving steadily from the frontiers of science into a new manufacturing mainstream.

a corresponding increase in the standard batch costs of about $500,000.

MAKING THE RIGHT COMPARISONS

Benchmarking can provide insightful transparency into what "good" looks like in a given industry and which dimensions should receive the most attention. In small-molecule, solid-dose manufacturing, the understanding is that a substantial share of the costs is variable (40 to 60 percent) and greatly linked to workforce optimization and productivity increases. In biomanufacturing, in contrast, the overall cost structure of a site is relatively inflexible, with relatively low variable costs. Hence, performance is strongly dependent on output volume and utilization levels. Although utilization is the most important factor, optimization is still possible on other dimensions.

Every path to success is different. As an example, one Asia-Pacific manufacturing site has been able to keep its costs low, its FTEs to a minimum, and its success rate high owing to a strong focus on process automation. In contrast, an EU site with a similar product focus has relied on high-quality, experienced personnel for its success to date. Although the site's personnel-cost share per standard batch is somewhat higher than average, it has nonetheless managed to keep its overall cost point in line with benchmarks and achieve effective operations, delivering good performance on most other dimensions (e.g., success rate, quality level and productivity).

Education

We have found that performance levels seem to be linked to the education levels of the workforce. Of course, the biomanufacturing industry in general tends to have a strong share of highly educated staff. Yet education levels vary widely. Across all sites, about nine-tenths of the workforce has some level of technical or life-science background — underscoring the importance of a scientific education to form the basis for effective operations. More interesting, at better-performing sites, more than one-fifth of the workforce has a master's degree or above, and at least three-fifths

has a bachelor's degree. In contrast, the worst-performing sites tend to have less educated staff, with closer to one-tenth of the workforce having master's degrees. One notable exception is a site at which we unearthed high performance, yet a workforce of which more than four-fifths lacked any higher education. Digging deeper, we discovered that this site's employees had among the highest tenures we have observed in the industry, with significant know-how developed on the ground over many years. As a result, we see a clear link between performance and education levels, especially if the average tenure at the site is low.

Capital Investment

It is often intuitively assumed that larger capital investments for a given amount of capacity will translate to better equipment and therefore higher manpower productivity and lower operating expenses. In biomanufacturing, however, that is not the case. Rather, we have observed limited to no correlation between the investment per installed fermentation capacity and either the manufacturing cost or the manpower productivity. In a few cases in which investments do seem to have delivered better infrastructure — for example, through increased automation — it has been difficult to verify performance improvement, usually because of underutilization. One exception is the previously mentioned site in Asia-Pacific, which has managed to realize value from its capital investment in automation by reaching top-quartile levels of utilization. In most other cases, the best-performing sites also have relatively low investment-per-installed-capacity profiles, while still emphasizing operational excellence. We therefore believe that in biopharma, how to invest is more important than how much to invest. This includes automation strategies that are deployed less for the sake of cutting costs and more to reduce human error, thereby drive quality outcomes. High-performing sites consume enough of a company's capital expenditure to create well-engineered facilities but do not overspend — confirming that good engineering is not over-engineering.

Quality Assurance Staffing

We have found no standard or consistency in the industry that can help to determine the most appropriate QA-staffing level. In fact, there is no correlation between the number of deviations and the size of the QA organization, nor between the number of deviations and the number of CAPAs; nonetheless, we have made two interesting observations. First, we have found a moderate negative correlation between the size of the QA organization and the frequency of breakdowns and infections, suggesting that increased QA oversight could drive down the frequency of these issues. For better or worse, the higher downtime linked to increased infections and breakdowns does not really affect the cost

The belief that improving one aspect of performance will harm another is generally incorrect.

point, most likely because this downtime is hidden in the idle-time buffer existing in most sites. Second, we have found some correlation between the number of QA personnel onsite and the level of CAPAs issued, hence indicating that CAPAs could be a proxy for QA workload and staffing requirements.

Scale & Labor

Among the many factors that potentially influence performance, we have found that the scale of operations has the greatest effect on costs, with an R2 of 0.7 correlating the costs per batch to the number of batches produced. Therefore, the more batches a site produces, the more competitive that site tends to be. After scale, labor productivity can have the biggest impact on unit costs. Labor costs in biomanufacturing are substantial, typically making up one-third to one-half of the total cost of a site. There is no primary department that generates the majority of these costs. The production workforce makes up anything between one-third and one-half of the total, while QA and quality control (QC) make up one-fourth to one-third and overhead and other production-support functions make up another one-fourth or so. As a result, labor productivity should be encouraged across the board.

NEXT STEPS

Management should determine each site's true performance potential relative to industry peers. Such a quantitative assessment may provide surprising revelations. For instance, the capacity a site can aspire to liberate can be substantial, whether through optimized changeovers (both product and campaign), improved management of unplanned downtime, better coordination of process steps or improved control of process variability. One company we observed was able to double its output from 50 to 100 batches in just one year by taking a leap of faith and challenging the current mode of operations: it increased the frequency of seeding and enhanced plant utilization, moving a sizable portion of its buffer time into manufacturing operation time.

Companies should begin by understanding the structural factors that define the maximum threshold of production performance in each of the relevant dimensions (output, lead time and quality). Structural limits are

higher than they are assumed to be, and current assumptions should be challenged in a constructive way.

Once the true structural ceiling is determined, variables can be optimized one by one, allowing the company to set and then progressively realign targets over time on the basis of realistic performance-improvement expectations.

Finally, the belief that improving one aspect of performance will harm another is generally incorrect. On the contrary, poor quality generally leads to high costs, while the pursuit of excellence brings benefits across the board.

As the biopharmaceuticals industry matures and becoming progressively more mainstream, its managers are beginning to take a new look at their operations, opening themselves to questions about improving both their technical and their operating performance. Those ready to commit themselves to the task today have the opportunity to get ahead of the industry tide that we see coming over the next few years. As they do, they are likely to attain a new level of performance excellence, one that will give them a competitive edge and establish them as top performers in the biomanufacturing industry.

Investments in Biopharma Production Continue

Investments in biologic capability are projected to fuel industry innovation

By Steve Kuehn, Executive Content Director, That's Nice LLC

Passing the second quarter of 2017, there seems to be little evidence that the biologics sector of pharma will slow down. Robust growth and expansion of the biologics market over the last few years has led to a highly competitive sector in manufacturing new biologic entities (NBEs) and biosimilars. Analysis from the 2017 Nice Insight Contract Development and Manufacturing Survey [1] found 51 percent of respondents were engaged in the development of NBEs, and 33 percent were engaged in the development of biosimilars.

BCC research finds the global biologics market is expected to grow 46.7 percent from 2014-2021, grossing an estimated $72.7 billion over the seven-year period, with monoclonal antibodies owning 53.4 percent of the market. Drivers for projected market increases said BCC include big brand-name drug patent expirations, growing incidence of chronic diseases globally, and increased availability of advanced diagnostics.[2]

The 2017 Nice Insight CDMO Outsourcing survey offers similar insight; the respondent product pipeline for biologics revealed vaccines are the most common product at 51 percent, followed by blood factors (46 percent), hormones (44 percent) and antibody drug conjugates (42 percent).

Industry watchers such as BioPlan Associates echo the sentiment. BioPlan's 13th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production revealed robust market stats and growing capacity capabilities not only

Robust growth of the biologics market has led to a highly competitive sector in manufacturing new biologic entities and biosimilars.

in established global markets, but also in emerging markets.

Capital continues to flood the sector, which continues to fuel tremendous growth. Eric Langer, president and managing partner for BioPlan Associates reports annual sales of biopharmaceuticals are now more than $200 billion globally, and industry revenue continues to grow at a rather steady ≤15 percent annually. This includes confirming an increasing number and percentage of pharmaceuticals entering the market are biopharmaceuticals, with about 40 percent of Big Pharma and overall pharmaceutical R&D/pipelines now involving biopharmaceuticals, not drugs (chemical substances).[3]

Lastly, the sector is winning. In 2015, the Center for Drug Evaluation and Research (CDER) approved 45 new molecular entity (NME) and new Biologics License Applications (BLAs), a peak number. In 2016, CDER approved 22 novel drugs, approved either as NMEs under New Drug Applications (NDAs) or as new therapeutic biologics under BLAs. But again, pipelines are full, so the pace, though moderating a bit of late, will stay steady.

Top companies are announcing significant expansions of capacity and technical ability. For instance, last fall, Catalent celebrated a new $34 million extension to its advanced Madison, Wisconsin, biologics manufacturing facility. Catalent announced that the additional 22,000 sq. ft. of space will accommodate a new 2 x 2,000-liter single-use bioreactor system. This will allow the company to accommodate late-phase clinical and commercial production of up to 4,000-liter batches. The new footprint will also support the expansion of analytical and process development laboratories, as well as additional office space. This expansion follows activity announced in 2015, including major expansion of its bioassay and protein characterization capabilities at its Kansas City facility and new integrated analytical capabilities at the Madison facility.

Similarly, German CDMO Rentschler Biotechnologie announced the opening of a

6,000-liter-capacity facility at the company's site in Laupheim. Revealing their confidence in the market's potential, the system increases Rentschler's manufacturing capacity for the second time within a year; a new 2,000-liter, single-use bioreactor was put into operation in 2015.

Earlier this year, Fujifilm Corp. announced the expansion of its BioCDMO division to increase production capacity and meet growing demand. The company revealed it has invested $130 million in its facilities in the United States and UK, including a $93 million cGMP production facility — built in part with funding from BARDA (Biomedical Advanced Research and Development Authority). According to Fujifilm, it has plans to invest an additional $28 million to outfit the facility with mammalian cell culture bioreactors and on 2018 projects. Fujifilm said the facility will manufacture the company's Saturn monoclonal antibody platform with an initial cell culture capacity of 6,000L.

Development and investment continue to flow into the biopharmaceutical sector, and 2017 will most likely end as another year marking the segment's trajectory.

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