

BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study

MANUFACTURING

The manufacturing portion of the benchmark study focused more on the operational aspect of production performance than on the technical science of the process. Best practices observed within and outside of the biopharmaceutical industry were

considered during the design of the study and subsequent interviews.

OVERALL IMPRESSIONS

In general, the idea of “Operations Excellence” is still in its infancy within the industry. Although many companies are in the midst of restructuring to help them become world-class manufacturing organizations, the reality is that they have a long way to go. The reasons for this are clear:

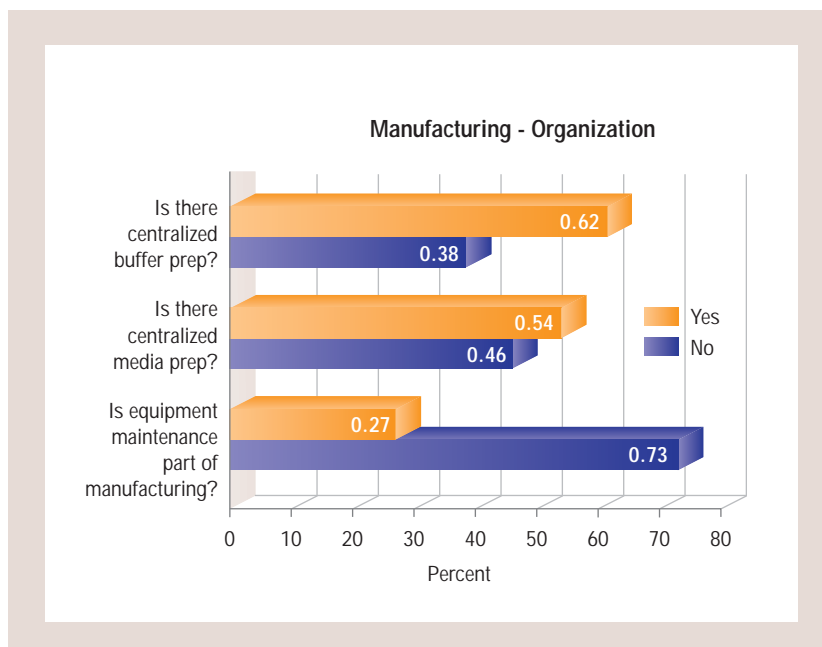
- There is, for the most part, limited competition solely on product cost and the ability to deliver. As a result, traditional outputs of lean operations, six sigma, and supply chain management programs are not yet the highest priority for the biopharmaceutical industry.
- Manufacturing is meeting the requirements. The market demand for product has yet to truly test the capability of the plants. Thus, the need for highly efficient and effective operations has not reached a critical point.

Nevertheless, the benchmark study highlighted many best practices. Some of the study data is provided below.

DATA ANALYSIS AND RESULTS

Organization

The structure of any organization, if not designed appropriately, can have a dramatic effect on performance. Every company participating in the study was organized by various production functionalities, i.e., fermentation was comprised



New Staffing Strategy Evolves in the BioPharmaceutical Industry

The lack of qualified human resources is one of the largest challenges facing biopharmaceutical companies in the United States today, for two reasons. First, the competition for talent is particularly difficult in clusters such as San Francisco, Boston, and North Carolina, where new sites and expansions can require hundreds of individuals trained in the industry's unique production systems and good manufacturing practices (GMPs).

A second challenge is the mixture of talent hired for production areas. Due to the historical complexity of biopharmaceutical manufacturing, companies tend to recruit bachelor-degree candidates, with the promise of transferring them to other company functions after one to two years in plant operations. This constant turnover of skilled resources, while valuable for other departments in a company, can wreak havoc on a production floor, resulting in costly mistakes and a large number of deviations.

This scarcity of resources and continuous turnover are driving companies to explore new hiring models to fill their manufacturing requirements. Most recently, these companies are looking to associate- and high school-degree individuals as the new breed of operators. The risk with this change is the potential increase in production mistakes and resulting deviations. Many legacy processes, although defined and validated, are not necessarily simple and often require operators to make frequent, on-the-spot decisions. Nevertheless, most companies are confident that this new staffing strategy, along with proper training, newer process designs, and modern plant automation will produce a minimal impact on the overall operation.

To support this transition, state-affiliated biotechnology industry organizations are working diligently to provide a mechanism for developing skilled resources for local companies. The Massachusetts Biotechnology Council is an organization aggressively supporting this concept through the Building Essential Skills Through Training (BEST) program. The program collectively recruits, screens, and helps train manufacturing technicians for a number of Boston area companies, such as Wyeth, Biogen, and Genzyme. Each company pays a nominal fee per applicant for the service. High-tech workers with process manufacturing experience, downsized during the dot-com slowdown, are successfully transitioning to the biotechnology industry through these programs.

Similarly, North Carolina offers the BioWork program, a 128-hour curriculum that provides training at local community colleges, as well as hands-on experience in industry-built and supported training plants. Many companies throughout the area send their new hires to this program as part of their standard training curricula.

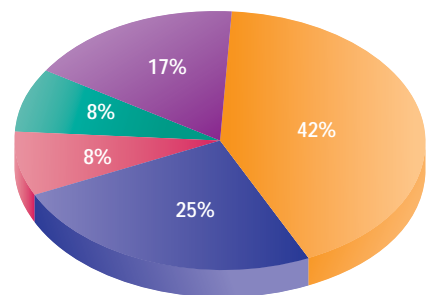
As with any industry, maturation of the technology, automation, and process will most likely minimize the need for college-educated production personnel. The key to ensuring high retention rates will be in developing a stable, skilled, GMP-educated workforce that expects to work in a production environment, and providing them with an appropriate level of job satisfaction through incentives and continuing education.

of dedicated fermentation operators, purification with dedicated purification operators, etc.

Within this functional structure, some companies elected to create specialized production support groups to help with operational activities, especially with media and buffer preparation. Experience shows that sometimes relying on the fermentation and purification operators to make the media and buffers, in addition to supporting ongoing production, can result in scheduling conflicts or mistakes that result in scrapped material. About one-half of the companies have a centralized group to support media and buffer preparation, with some organizations centralizing buffer preparation only (which is a more complex operation in most plants). This centralized group often will support equipment cleaning and staging, working with the production planner to assure the appropriate availability of equipment and materials when production is ready to start.

Another structural decision many companies make regarding the production operation is the reporting structure of the equipment maintenance operators. The study indicates that the preferred location of this group is within the facilities/engineering part of the operation, rather than reporting to manufacturing. The resulting advantage, especially for smaller companies, is a greater efficiency with resources (by sharing them with facilities support.) A downside of this structure is that manufacturing can potentially lose control of the support resources that focus on keeping equipment operating. These priority conflicts tend to be more pronounced in fill/finish operations, which operate at higher speeds and have

Fermentation - Shift Structures



24/7 - 10-Hour shifts Non 24/7
24/7 - 8-Hour shifts 24/7 - 2/3/2
24/7 - 4/3

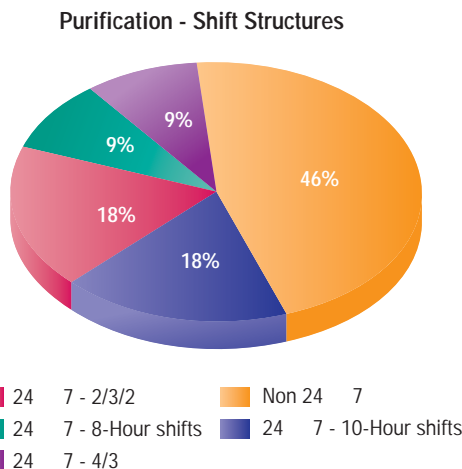
more downtime issues. Most high-performing companies in other industries locate their maintenance function within the manufacturing organization to minimize these issues.

Staffing

A little more than one-half of the participating companies currently require 24-hour coverage in bulk production. The move to a 24x7 operation can be a challenge to many operations, and the appropriate shift structure is often a point of extensive discussion. There appears to be no standard or preferred shift structure for full-time operations. However, individuals in companies using the 2/3/2 type structure were more positive about the benefits than those from companies using other 24-hour formats. Additionally, maintaining stable shifts, i.e., not moving from night to day regularly, was another factor that many felt was important to employee satisfaction.

An analysis of the education levels of biopharmaceutical operators comes as no surprise – the inherent complexity of bulk production operations have traditionally required higher-educated employees who can make decisions on the floor, as well as develop production documentation. Purification, the most complex part of the production process, has the most educated workforce, while packaging has the lowest-educated staff.

Turnover statistics reflect the difficulty in retaining employees, not only in the entire organi-

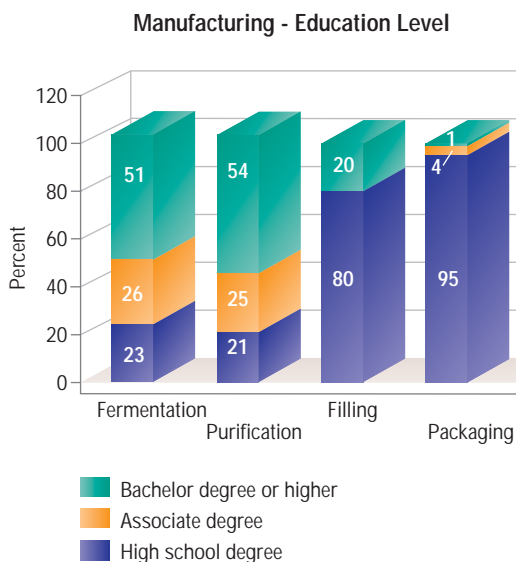


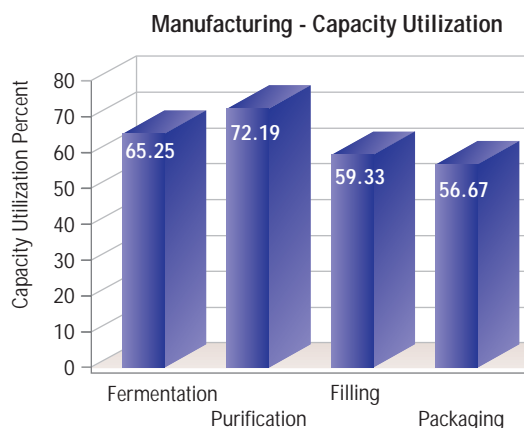
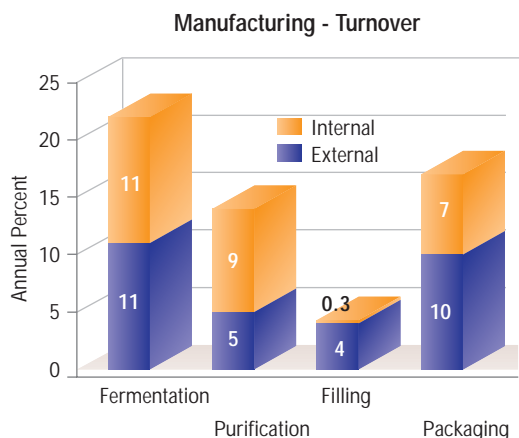
zation but within manufacturing departments. The highly competitive nature of the business is a contributor to this phenomenon. Most companies realize, by the very nature of their hiring practices, that the bulk production areas are feeders to other parts of the organization. Fermentation, often the entry point for bachelor-degree candidates, tends to lose operators either to other parts of the company or into purification on a relatively frequent basis. The more complex and challenging nature of purification seems to retain operators better. Like fermentation, they tend to lose one in ten to other internal roles, mostly to the quality department.

Systems

Most world-class production operations in other industries have a significant amount of information on operating performance. Typically, biopharmaceutical companies have highly detailed information on process performance, as good manufacturing process (GMP) requires control of these parameters. However, performance tracking systems, like MES or custom databases to manage the production schedule and operator efficiency, are not as common. Again, the luxury of less-than-full capacity utilization results in a limited need for minute-by-minute accounting of line status. Should demand ramp significantly, a detailed understanding of daily activities and operator performance will be crucial to maximizing uptime.

Looking at the statistics, filling and packaging areas are more likely to have tracking systems in place. This is primarily because repetitive, high-speed functionality lends itself to that type of tracking.





Performance

Overall, production capacity in the industry is not fully utilized. Utilization is defined in this study as the percentage of available hours an area is used once periodic maintenance, shutdowns, and holidays have been taken into account. In this case, 100% utilization is theoretically possible with perfect efficiency. Purification is described as the bottleneck of most organizations, but even that area was not always used at full capacity. When there is less utilization of capacity, there is less intensity and focus placed on maximizing every hour of production performed.

Fermentation changeover times, one of the few key parameters impacting the throughput and performance of production, were collected during the study. Companies were able to

change over between different products in about 178 hours, on average, ranging from 35 to 408 hours. Two types of companies reported shorter times – those that specialize in contract production requiring regular changeovers, and those with more modern plants designed for efficiency. Overall, companies tend to plan for approximately one week between products. If production requirements increase, changeover reduction should be a main area for companies to focus on to improve capacity capabilities.

From a quality perspective, manufacturing is one of the key contributors to deviations. In companies that were able to provide the detail of the source of deviations, 63% of all deviations were attributed to manufacturing.

