

BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study

OVERVIEW

WHERE IS THE INDUSTRY HEADED?

The biopharmaceutical industry is undergoing a transition. After recently celebrating the 21st anniversary of the first approved biotechnology drug, there are now dozens of approved drugs in the market with many more in the pipeline. As the industry matures, the form biopharmaceutical companies will take is yet to be determined. Will they develop more like their big brothers, the traditional small-molecule manufacturers? Will they be swallowed up by these large companies and become just another technology center for multinational therapeutic companies? Or will they diverge and become factory-less companies, similar to their high-tech counterparts, focusing on development and innovation and leaving the production side of the business to contract manufacturing companies?

One thing for certain about the industry is that current limited direct competition and minimal focus on costs and efficiency will not continue for long. With the growing number of therapies in development and the certainty that biogenerics are a short time off, it will become vital for biopharmaceutical companies to implement world-class development and production strategies if they wish to sustain a competitive advantage and fully capitalize on new product development.

Even before these major trends evolve, some forward-thinking companies within the industry are already preparing for this competitive future by beginning to concentrate on operations excellence. Now that they realize they can produce these difficult products – and do it consistently – they are searching for methods to improve overall performance, primarily in their quality systems and processes. Additionally, there has been a constant stream of new talent entering the biopharmaceutical field from large pharmaceutical companies that adopted operations excellence concepts throughout prior years. High-tech industries hit hard by the economic downturn also have contributed to the talent pool. These individuals recognize the inefficiencies that have developed in the organically developed biopharmaceutical industry, and they are equipped with the experience to improve the business without reinventing the wheel.

Another motivating factor for change is based on the complicated manner in which current inefficient business practices evolved – many were established in an attempt to increase compliance and prevent deviations, thereby creating more complexity and more regulatory concerns. Consequently, most companies in the industry are using the upcoming Code of Federal Regulations (CFR) revisions as the impetus for dramatic change to quality systems.

The constantly evolving use of technology to manage product manufacturing and quality processes is another driver of change. Recent strides in web-based, easily configurable 21 CFR Part 11-compliant systems can make the automation of key business processes relatively straightforward and cost effective.

These factors have resulted in an industry that is ready for change and still willing to share operational practices with the hope of enhancing its overall performance.

THE OPERATIONS EXCELLENCE CONSORTIUM

One acknowledgment of this expected trend is the formation of the Operations Excellence Consortium, a group of industry executives and managers that meets on a quarterly basis to informally benchmark operational challenges and propose solutions. The consortium, which includes representatives from manufacturing, quality assurance, quality control, and supply chain areas, addresses cross-functional business processes focused on making and delivering product in the most effective and efficient way.

Discussions about operations excellence in the biopharmaceutical industry inevitably lead to its comparison with the traditional small-molecule pharmaceutical industry. The reasoning goes: Both industries produce drugs, they are constrained by the same regulations, and now the same arm of the U.S. Food & Drug Administration regulates the two. In fact, much of the equipment, automation, and staff in biopharmaceuticals were adapted from traditional pharmaceuticals. As a result, why should we expect their differences to be that great?

Experience working with 15 of the top 30 pharmaceutical companies and eight of the top 10 biopharmaceutical companies confirms there are important differences that distinguish each business from the other.

One of the key differences is product consistency. Biopharmaceuticals work with a substrate and raw material that are inherently unpredictable: living cells. Each batch of product produced in fermentation can be slightly different from the last, even when all process parameters are kept stable. This complexity leads to more convoluted manufacturing instructions, resulting in hundreds of pages of records per batch. Pharmaceutical companies, which use chemical manufacturing techniques, have a much more repeatable and predictable process and simpler batch records.

The complexity in biopharmaceutical processes results in the need for more robust

quality systems. The difficult production process creates a higher number of deviations and investigations, sometime many per batch. These errors range from significant events that threaten the product to documentation mistakes resulting from the long, challenging batch records.

Pharmaceutical batches, on the other hand, have a much smaller number of deviations that often can be quickly resolved. The fewer number of investigations, the shorter the cycle time for lot release. Historical data show that traditional pharmaceutical releases of 10 to 14 days are significantly less than biopharmaceutical releases of 80 to 90 days.

Another key differentiator between the two businesses is the analytical testing required before the product can be released to the market. Again, the complexity of biopharmaceutical proteins requires much more involved and time-consuming testing to characterize the molecules. Additionally, since most biopharmaceutical products are parenteral, additional sterility testing is required. This additional testing not only results in longer cycle times, but also more opportunities for inefficiencies and errors.

In addition to the technical issues that differentiate these industries, the lack of generic competition to biopharmaceutical companies created a significantly different business model. This protection allowed the industry to focus more on research and development rather than on building high-efficiency, low-cost, low-cycle-time companies. For traditional pharmaceutical manufacturers, high efficiencies are key to capitalizing on market opportunities early and capturing a healthy market share.

Nevertheless, biopharmaceutical manufacturers can learn much from the more mature pharmaceutical companies who, over the years, have discovered and systematically removed inefficiencies. Benchmarking with the traditional pharmaceutical industry on a numerical level may not be appropriate, but the adaptation of best practices can be highly valuable to this maturing industry.

In an effort to formalize the information sharing and structure a method to identify best practices, the consortium membership chartered Tefen in mid-2002 with the task of conducting an industry-wide operations BioBenchmark study. The participants believe that the data and conclusions gener-

Study Set-up

- Identify key benchmarking areas with Operations Excellence Consortium input
- Recruit participating companies
- Design questionnaires

Data Collection

- Send forms to participating companies
- Perform on-site interviews to collect data

Data Analysis

- Verified collected data with participating companies
- Identify best practices and industry trends

Final Report

- Host one-day review of results with participating organizations

**BioBenchmark Study
Methodology**

BioBenchmark Study Participants

- Abbott Bioresearch Center
- Chiron Corp.
- Wyeth Biopharma
- Amgen Inc.
- IDEC Corp.
- Lonza Biologics, Inc.
- Genzyme Corp.
- DSM (Biologics, Pharmaceuticals)
- Biogen, Inc.
- Abgenix, Inc.
- Gilead Sciences, Inc.
- Diosynth Biotechnology

ated through such a study will be vital for guiding improvement within their organizations.

The purpose of the study is to offer benefits to companies of all sizes. Larger companies with at least one marketed product will gain insight into their operational performance and have a basis for comparison with their peers. And smaller companies planning for future growth will have an overview of the industry's operational challenges and trends to use as a roadmap to operational excellence.

STUDY DESIGN AND METHODOLOGY

Tefen and the consortium members co-developed the study's design, which consisted of two parts.

Part I

Part I of the study focused on collecting performance information for the 15 key functions most critical to the "Make Product" process, including:

- **Manufacturing**
 - Fermentation
 - Purification
 - Filling
 - Packaging
 - Planning and Control
 - Equipment Maintenance
- **Quality Assurance**
 - Release (disposition)
 - Deviation Management
 - Change Control
 - Document Management
- **Quality Control**
 - Raw Materials
 - In-Process
 - Facility Monitoring
 - Product Testing
 - Stability

A questionnaire was developed for each function, capturing both qualitative and quantitative data for later analysis. As important as numerical

data is, the ability to compare how different business practices impact these metrics was an important goal of the study. Overall, the study included nearly 1600 questions, focusing on areas such as business processes, work methods, organizational structures, electronic systems, labor, metrics, and supporting systems.

A total of 16 different biopharmaceutical manufacturing sites, representing 12 different leading companies, participated in the study through on-site interviews conducted by Tefen subject matter experts. The study results included identification of performance metric averages, best performers, best practices, and main gaps for each participating company. Industry trends and common practices were highlighted and, where needed, a recommendation for a more detailed evaluation was provided to each participating company through a series of customized reports. Confidentiality of individual company data was maintained throughout the process.

Part II

Approximately 30 industry executives were surveyed during Part II of the study to gain an overview of the industry through the eyes of its leaders. Vice presidents and executive vice presidents provided their opinions of overall industry trends, future developments, and main challenges and objectives. The Executive Summary is the result of their input.

STUDY RESULTS

A sample of preliminary data from both parts of the benchmark study is included in this supplement. With over 1600 data points in the study, not all could be presented here. However, the key data points presented provide an excellent overview of where the industry currently stands and what the future might bring.