Supplier-integrated support of biopharmaceutical raw material systems promotes operational excellence and risk mitigation

Abstract
The biopharmaceutical industry is increasingly engaged with concerns about operational excellence, safety and risk mitigation. These issues have historically affected large-scale pharmaceutical manufacturing but now are gaining prominence throughout biological production scale-up and process transfer. SAFC® provides biopharmaceutical clients with supply chain solutions through novel applications of vendor-partnered capabilities. This paper presents strategic approaches to biopharmaceutical process optimization through supplier integration that maximize revenue, reduce costs and support reproducibility of production processes. It also describes how vendor-partnered solutions deliver leaner and safer processes for raw material handling.

Introduction
The biopharmaceutical industry is experiencing a new paradigm in which risk mitigation and operational excellence are prevalent trends. It is no longer enough to develop and produce a blockbuster drug candidate; it is now critical to effectively manage costs, in-process quality, operational safety and supply chain security.

No longer is it important to just develop and produce a blockbuster drug candidate.

To help manage the complexity, SAFC offers strategic supply chain solutions that assure batch quality and consistency during manufacture, support complex regulatory compliance and reduce shipping delays, so you stay on time to market and maximize financial results.

The challenge for biopharmaceutical manufacturers to become more efficient and safe is daunting, considering the large number of raw materials required for production and the complexities of cell culture systems. However, this challenge can be overcome if manufacturers partner with knowledgeable and experienced suppliers early in process development.

The challenge
Unlike small-molecule pharmaceutical for which a chemical reaction remains relatively constant through production scale-up, bench-top biopharmaceutical experiments are not necessarily linear to large-scale manufacture because the processes are much more complex. Biopharmaceutical processes require stepwise technology transfers, often with unique processing steps, in order to ensure that the same product is produced at large scale as at small scale. This stepwise process makes developing biopharmaceutical processes expensive and time-consuming and highlights the need for producers to investigate integrated supply chain solutions early in the development process to ensure cost-effective, safe, and reproducible systems.

Recent industry conferences have presented many examples of the impact of increased costs from biopharmaceutical technology transfer and added production system complexities. These presentations have shown that raw material costs are now less of a concern than the overall operational costs for determining and applying process steps.
Unchecked variability in technology transfer and production make it difficult to effectively manage production resources. Assume, for example, that a 10,000 L production tank is worth about $10 million in drug product. +/- 10% due to raw material or process variability translates into +/- $1 million in final product.

If capacity and resource constraints limit cell culture and purification runs by 10% a year, a potential of $50 million in loss revenue is at risk and/or may lead to increased production costs from outsourcing production to a contract manufacturer.

- How can resources be maximized?
- How can secure supplies of raw materials be maintained?
- How can suppliers be better integrated into overall processes?

Adding to the challenge of complex biopharmaceutical systems is the desire for manufacturing facilities to be more flexible. The reality is that more clinical projects are filling the pipeline, but fewer on-site resources are available to maximize production output.

Below is an example of the complexity that faces biopharmaceutical production engineers. Steps required for production in mammalian-based system can include several feed additions that require time point-specific supplementation:

The impact on the manufacturing routine of adding multiple components to the production system is not completely understood until the entire operational process is reviewed. This full process includes initial receipt and preparation of raw materials, quality control testing and charging components for manufacture.

Each step pictured on the following page details the Total Cost of Ownership (TCO) for each raw material incorporated into the production process, including:

- Logistics, sourcing and documentation
- Inbound receiving steps
- Unit sampling
- QC testing
- Inventory and tracking
- Media hydration and clean-up time

### The integrated supplier approach

In a February 2006 BioProcess International article, "Managing a Biopharmaceutical Supply Chain," Allen Jacques, Senior Director of BioPharma Supply Chain at Wyeth, points out the differences and complexities between classical pharmaceutical production systems and present day biopharmaceutical systems. His point is illustrated in the following image (see next page) that compares molecule sizes of the rheumatoid arthritis biopharmaceutical, ENBREL, to the legacy small molecule drug Ibuprofen.
This statement holds true for all elements of supply chain and manufacturing. Creativity is required to remove constraints currently inhibiting process optimization and open opportunities for cost savings, enhanced reproducibility of production processes, and greater safety.

"It is easy to focus on such differences in our industry as reasons why classical supply chain principles do not apply. I suggest they are applicable; they just need to be applied with a measure of creativity."

Allen Jacques, Wyeth

Creative supply chain solutions are best achieved when potential suppliers are integrated early-on into manufacturing processes. For many organizations, this means during process development. At this point, suppliers and manufacturers can become intimately connected in a focused approach to long-term process and resource optimization. This interconnected focus approach allows biopharmaceutical manufacturers to backwards-integrate with suppliers, positively influencing the direction and effectiveness of supplier-partner solutions.

Understanding the following process scenario is required before actively pursuing and integrating suppliers into your production processes:

- **Map** your entire process from development through theoretical production scale
- **Identify** the points where suppliers currently touch your process
- **Identify** areas on the map that currently cause constraints
- **Begin** scenario planning to identify the most likely, and worst, operation cases that may affect your process efficiency and safety
Identify
1. How much drug product will be required for clinical trials?
2. How much drug product will be required for market commercialization?
3. How robust and effective is your current process in meeting production goals?
4. What is your production capacity?
5. What additional process development steps may be required to reach your production goals?
6. What is the outlook for your Bill of Materials (BOM)?
7. How will additional raw material requirements and processing steps affect your Total Cost of Ownership?

Process diagram presented by Sartorius Stedim Biotech
Once you understand the various scenarios that may impact your commercialization process, you can begin identifying those suppliers best positioned to enhance your production and operational goals. Use the following criteria:
1. What are your BOM needs?
2. Which suppliers provide the majority of your BOM needs?
3. What are your operational constraints regarding raw material supply and production utilization?
4. Which suppliers are focused on the industrial cell culture market and can provide custom solutions for your application?
5. Which suppliers have risk mitigation practices similar to your own?
6. Which suppliers can integrate with other suppliers to provide the optimal solution?

Proven results
A biopharmaceutical manufacturer for whom SAFC is a primary supplier of critical raw materials requested that we work to develop a solution to an operational challenge they posed:

Challenge
- Enhance logistic operations capacity
  - Drum dumping process not optimized
  - Dispensing 3,500 kg
  - 7,000 repetitions

Solution
- New filling regime and supplier-managed net weighing
  - Removed two non-value steps

Powder Filling Machine
Servo Driven Auger Filler
- Programmable Logic Control Scale Feedback
- Multiple Tooling Sets
Benefits

- **Reduced ergonomic safety risks and non-core labor hours**
  - Reduced customer dispensing steps by 50%; reduced handling exposure
  - Reduced wasted labor hours from 80 to less than 20 a week

Recognizing the value of this supplier-integrated relationship, the customer asked how SAFC could further improve manufacturing efficiency and supply chain security. This launched a new collaborative effort in which:

- Raw material risk mitigation steps have been defined for each raw material in the media formulation
- A three-phase dry powder media transfer approach has been recommended, consisting of:
  **Phase 1**: A powder transfer bag system to ensure powder delivery and safety in a timely manner
  **Phase 2**: A drum dumper process that relieves manual addition steps
  **Phase 3**: Design and application of a flexible bulk intermediate contaminant unit to provide as few as one media addition steps, reducing QC sampling requirements and personnel handling steps. Note: Final phase requires capability development and continual collaboration

SAFC integrated supplier approach

SAFC offers the world’s broadest range of products, services and capabilities for the biopharmaceutical industry. SAFC partners with other suppliers, including Sartorius Stedim Biotech, Vivalis and Novozymes, to provide integrated solutions that impart unmatched value to the industry.

To learn more about examples of how SAFC has integrated with manufacturers to enhance production efficiency, supply chain security and operational safety, visit www.safcglobal.com