FEEDING THE CELLULAR FACTORY: MANAGING SUPPLY CHAINS IN THE BIOPHARMACEUTICAL INDUSTRY

INTRODUCTION

Biopharmaceuticals are a fast-growing segment of the pharmaceutical industry, with more than 200 drugs in this class approved for use in the past 3 decades.[1] It is a diverse category that includes antibodies, signaling proteins, and enzymes. Biopharmaceuticals have great potential and numerous applications in therapies for rare and previously untreatable diseases, as well as throughout the field of medicine.

Biopharmaceuticals differ from more traditional small-molecule drugs, both in their immense size and in the way they are made. Biopharmaceuticals boast molecular masses in the dozens or even hundreds of kilodaltons—so large that

A specialist enters one of the ISO-Class 8 packing suites at the 150,000 sq ft Spectrum facility in New Brunswick, NJ.

Image credit: Spectrum

it's impractical or impossible to manufacture them by traditional chemical synthesis methods. Instead, they are manufactured within living cells that have been genetically modified and repurposed as tiny molecular factories.[2]

Living factories, of course, require different types of raw materials from those used in the production of conventional pharmaceuticals. The manufacture of biopharmaceuticals demands whole categories of reagents for growing, feeding, and harvesting the cells. And it doesn't end there: a large variety of reagents are also needed for isolating a single drug molecule from among the many molecules, both large and small, found in cells. As biopharmaceuticals continue to gain recognition and an increasing share of the market, the sourcing and delivery of these reagents has become almost an industry unto itself. As the field matures, suppliers are offering more and higher-quality services to biopharmaceutical companies. Selecting a reliable and competent supply partner hinges on understanding the demands and constraints that are specific to the biopharmaceutical industry.

INCREASING COMPLEXITY OF SUPPLY CHAINS

When dealing with small molecules—a general term for the class of pharmaceuticals small enough to be manufactured by organic synthesis methods—the bill of materials for manufacturing a drug product might consist of a few dozen entries. That list would encompass the starting materials, reagents, and solvents that go into constructing the molecule, along with a few inactive ingredients (excipients) that accompany the drug into its final dosage form. The early stages of the drug's synthetic route might be carried out by a contract manufacturer, while the final synthesis steps and formulation are done elsewhere. With contract manufacturers overseeing more and more of the supply chain, the firm that formulates and markets the drug product will see its raw materials list shrink accordingly, says Jim Luchsinger, vice president of business development and international distribution at Spectrum Chemical.

Biopharmaceutical manufacturing shares these same trends in outsourcing, but the overall list of raw materials is considerably longer, sometimes encompassing more than 100 items.

The list of raw materials begins with the cell line. Makers of biopharmaceuticals put a great deal of effort into finding the optimal microbial or mammalian cell that is capable of producing the desired molecule. Once identified, this cell line will be fermented in sterile growth media and harvested by mechanically rupturing the cells to release their contents. The resulting biological soup will be centrifuged, extracted, and then purified to isolate the biopharmaceutical, then mixed with filler compounds and sterile buffers to produce a finished drug product.[1]

Cell growth media alone may contain dozens of discrete ingredients, Luchsinger explains. Productive, well-balanced nutrient media are a must in keeping cell lines well fed.

In addition to the ingredient lists for biopharmaceutical manufacturing being longer, the individual materials are often subject to more stringent quality and purity demands. In the world of drug manufacturing, this means adhering to good manufacturing practices (GMP), the set of rules and guidelines meant to ensure quality and purity in pharmaceuticals. In a small-molecule manufacturing process, non-GMP-grade materials are chemically altered under harsh solvent and temperature conditions—thus minimizing the risk of microbial contamination—to form a GMP-grade final product. But that is not always the case in biopharmaceutical processes, where many reagents will not end up incorporated into the structure of the drug molecule. Quality assurance departments, as well as regulatory agencies, may therefore require that those raw materials be GMP from the start, Luchsinger says.

Biopharmaceuticals also require a lengthy and rigorous purification process in which the cell harvest is purified through multiple rounds of chromatography and filtration steps. Along with the formulation of the biopharmaceutical into a finished dosage form, these steps are collectively referred to as downstream processing.[3] Even though the buffers and other materials used in these downstream steps are not incorporated into the chemical structure of the biopharmaceutical, they tend to be saddled with a higher regulatory burden."Those chemicals, those buffers, are touching the final protein in the downstream purification," Luchsinger explains. As a consequence, most manufacturers will require a GMP-grade material that complies with exhaustive specifications.

PARTNERING EARLY IN THE SUPPLY CHAIN

Biopharmaceutical processes can be sensitive to minuscule amounts of contaminants and impurities. Trace levels of metallic impurities in buffer salts, organic impurities leached from plastic processing equipment, or even something as innocuous as an improperly mixed cell growth media can cause unpredictable batch-to-batch variation.[4]

Growth media is a good example of what makes biopharmaceutical raw materials hard to standardize and control. Most of them are a proprietary blend, optimized for one particular cell line. In fact, large suppliers may employ whole research groups with the optimization of growth media as their sole focus, says David Feldker, a consultant to the biopharmaceutical industry. "They take someone's cell line and they grow it," Feldker adds."They keep changing nutrients and time and temperature, all those different factors, and they may spend a year or two optimizing that growth rate so the cells can produce" as much of the drug as possible.

Biopharmaceutical companies also rely on their suppliers to carry out some or all of the rigorous testing that regulatory agencies require. To protect the health of their customers, companies are likely to opt for the safest route and require full monograph testing, carrying out the full litany of tests laid out by the US Pharmacopeia (USP) in its monograph for each item used in

Spectrum maintains four on-site analytical testing laboratories and performs over 20,000 lab tests each year to ensure ingredient safety.

Image credit: Spectrum

the biopharmaceutical manufacturing process. There can be as many as 25 distinct tests for a single item, Feldker says, so it's important to choose a supplier with the right analytical instruments and resources to carry out those tests. Biopharmaceutical firms may also take a more hands-on approach by collaborating with the supplier to exclude impurities.[5]

"For excipients in particular—where you're one step away from patients—we take a very hard look at what the specifications are that the supplier finds acceptable," says Ken Hawkins, senior director of network strategy at Sarepta Therapeutics. "Then we need to make sure it will be acceptable for our product." Often, he says, "we have to work with suppliers to develop custom specifications."

PACKAGING CONCERNS

Once the raw materials are sourced, companies have to address how they will be packaged and stored. "If you're building a new facility, the warehouse needs to be bigger than it did 20 years ago," says Matthew Olsen, manager of fluid management technologies for North America at Sartorius Stedim Biotech. That is due in part to the industry's demanding appetite for raw materials (hungry cells consume a lot of growth media) but also to the advent of single-use production equipment. Where production sites were once dominated by stainless steel bioreactors in a fixed configuration, new installations feature single-use plastic bags held in place by steel frameworks.

"People are moving toward what they call the ballroom concept, which is where you just basically have a clean room—it's a big clean room," Olsen says. The large, open-concept clean room allows manufacturers to rearrange their equipment as necessary for any given process. The ballroom design saves time and money by reducing the need to manually wash and sterilize the equipment between batches. It also makes manufacturing sites more flexible in enabling them to pivot between the several chemical entities a company may have in its pipeline.

Single-use production equipment may be the wave of the future, but manufacturers of final active pharmaceutical ingredients are hardly the first to explore that frontier. Raw materials have been supplied in single-use packaging for more than a decade. There are still strict requirements for what that packaging can be made of—namely, it must almost always be plastic, says Olsen.

These stringent requirements have created a healthy demand in the industry for repackaging services. Luchsinger at Spectrum gives the example of Budenheim, a German producer of phosphate salts.

Companies such as Budenheim have a diverse customer base, with biopharmaceutical companies representing a relatively small share of their overall demand, so it isn't economical for firms like these to provide the more expensive resealable plastic packaging that the biopharmaceutical industry requires. Instead, as happens with many bulk powdered chemicals, Budenheim packages its products in a paper tube that can be filled in seconds and sealed on both ends, Luchsinger explains.

Those paper sacks can't be brought into a biopharmaceutical manufacturing clean room because they run the risk of introducing foreign contaminants and microbes. Wood pallets and fiber kegs are out of the question for the same reason. Instead, the biopharmaceutical industry opts for polyethylene pails, which can be sanitized to avoid contaminating clean rooms, says Luchsinger.

CHOOSING THE RIGHT SUPPLIER

Like any other manufacturing business, the biopharmaceutical industry benefits from minimizing unpredictability. This principle becomes even more important when the "factory" is as crowded and incompletely understood as the inside of a living cell. Cells are sensitive to changes in their environment and may alter their biological processes in response to different nutrient or impurity levels, and that can result in a biopharmaceutical product that behaves differently.[6] With this in mind, scientists attempt to stamp out batch-to-batch variation anywhere they can.

With biological systems, "we have lots of batch-to-batch variability," notes Tugce Martagan at Eindhoven University of Technology. "Even if everything is perfectly controlled, even if you do the same recipe and monitor the process very closely and have an identical environment in each and every batch, you can still have lots of variability and lots of uncertainty."

All raw materials and finished goods entering Spectrum facilities are subject to stringent in-house testing.

Image credit: Spectrum

Even perfecting all scientific aspects of a process would by itself not lead to optimal manufacturing; the business decisions affecting that process must be considered. Once begun, many biopharmaceutical processes cannot easily be paused or postponed while waiting for materials to arrive. This "no wait time" requirement, as Martagan puts it, is idiosyncratic to chemical manufacturing in general and to biopharmaceuticals in particular. To begin with, the cells themselves must be harvested at the optimal moment—after they have reached a high concentration but before they begin to die off. Once the cells are harvested, the biopharmaceuticals themselves tend to degrade over time. Proteins and other therapeutic molecules are by design somewhat chemically active and prone to oxidation or side reactions when in the presence of air and moisture. Unfortunately, these describe the primary conditions necessary for downstream processing. Biopharmaceuticals must therefore be carried through downstream purification and formulation steps as quickly as possible and be stored at low temperatures between steps, Martagan says, adding "You have to make sure that each and every piece of equipment, and each and every raw material, will be ready." In practice, this means working with suppliers to shorten lead times and establish a reliable source, or building some redundancy into the supply network by choosing a supplier with access to multiple sources for the material.

"If something comes up as a critical raw material or a supplier is a critical manufacturer for you, it makes a lot of sense to evaluate redundancy," says Hawkins at Sarepta. Companies might qualify two suppliers and use them interchangeably or use one firm as a primary supplier and qualify a second as a backup. The suppliers should be based in different regions to minimize susceptibility to supply chain disruptions, such as those caused by the COVID-19 pandemic, Hawkins explains.

CONCLUSION

The explosion of biopharmaceuticals in the past few decades has created new challenges for the industry's suppliers. Many and diverse raw materials are needed to produce a biopharmaceutical, and they are highly regulated worldwide. Supply partners with biopharmaceutical expertise are vital to the process; they should be able to purify reagents and put them into appropriate packaging as well as provide testing and a guarantee of quality. By building a strong relationship with suppliers, biopharmaceutical companies can control the critical parameters that make their process run smoothly in order to ensure a steady supply of reliable product for their customers: patients who depend on their product for treatment.

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