Minimizing Costs and Process Times with Local Biomanufacturing

by Maribel Rios

For a growing number of biopharmaceutical companies, the world is getting smaller. They are operating in smaller, more flexible facilities; servicing potentially smaller markets; and managing local products. Local manufacturers are looking for ways of doing standard processing less expensively without making changes that carry regulatory risk. Most of these facilities are vaccine manufacturing sites. The upsurge in localized diseases and need for global pandemic preparedness (especially under uncertain capacities) have countries such as Malaysia, India, China, and Brazil pushing for local production plants to supply vaccines and other drugs. Legislative and social changes such as US healthcare reform, worldwide recessions, and the push for increasing biosimilars are driving the need for greater manufacturing efficiency. To become more efficient in processing, localized manufacturers will need to become aware of the impact of social, legislative, and technology factors that are fueling this trend toward decentralized manufacturing.

An upstream scientist works with a 1,000-L single-use bioreactor at Laureate Pharma
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Does Local Manufacturing Make Economic Sense?

Whether it makes economic sense to manufacture biopharmaceuticals in a smaller, emerging market depends heavily on production efficiency. Making a drug locally must be less expensive than importing finished products on the open market.

In a 2005 position paper, Warren Kaplan, assistant professor at Boston University's School of Public Health, and Richard Laing, medical officer for the World Health Organization, explain: "This sets up the inherent tension between a health policy directed to the access problem of making available low cost and quality-assured medicines and an industrial (primarily private sector) policy of optimizing profits and growth by promoting a local industry whose products may be more expensive than those on the international market" **(1)**. The authors conclude that India and Brazil are examples of large countries with well-developed "indigenous" pharmaceutical industries and thus are capable of producing cheap, assured quality drugs.

However, smaller countries with fewer resources and a weak industrial base are unlikely to be viable in the global pharmaceutical market. In fact the authors state that there are definitely regions where the local manufacture of drugs does not make economic sense and in some cases may restrict the access to high-quality medicines because producing in multiple countries "forgoes the economy of scale."

Some companies are concerned that producing for a small market will be too expensive because of regulatory and quality overhead, the cost for ensuring product safety, and the cost for ensuring protection of intellectual property. Matthew K. Hudes, US managing principal of biotechnology at Deloitte Services LP, suggests that biopharmaceutical manufacturers learn from the electronics industry, which 20 years ago had many of the same concerns regarding intellectual property protection and manufacturing costs. "They viewed it as a long-term strategic commitment. It was always on the agenda to be global and be in those locations, and I think the same is true for life science companies. Governments want those drugs available for their population where it is appropriate."

Localized manufacturers will need to keep a close eye on the changing market in various regions. "Everyone wants to know what's the next biotech hot spot or cluster," says Hudes. "I really don't think that is relevant anymore because what we're seeing now is what we saw in the high tech and electronics industry about 20 years ago, which is specialization by region. If you take a look at the value chain of manufacturing of the whole life science business, I think you are going to see expertise built up in certain areas. So I think we are going to see certain capabilities in India, certain capabilities in China, and other areas such as Singapore."

Although the pace of technology advancement has made it easier for companies to set up manufacturing in developing countries, there are still real-world costs of operations as well as local and global health policies and regulations to be addressed. "The biggest challenge is probably getting skilled labor," says Michiel Ultee, vice president of process sciences at Laureat Pharma. "Biopharmaceutical skill level is higher than smaller molecules because it's more complex."

Tom Ransohoff, vice president and senior consultant, at Bioprocess Technology Consultants, agrees, "Most of the costs of running a facility in this industry for most products are fixed, such as labor and energy. If you have a smaller market, your cost structure is not going to be as good as someone who is making a product globally, so there have to be other reasons that justify setting up manufacturing locally. For most of medicines, it doesn't make sense to have a lot of small facilities. Local manufacturing, however, is important for small volume products, products for only a local market, or just for clinical trials."

One of the most important factors for an emerging market is building an a experience and expertise base, primarily through ensuring regulatory review. "You can build the best facility in the world and have the best science with that facility, but if you don't have regulatory review, it doesn't matter, you can't make a product there," says Hudes.

Watching the Biosimilars Market

Slimming down costs means keeping up to date with changes in regional markets, including how a region may be influenced by the penetration of biosimilars is the market. Matthew Hudes of Deloitte Services offers his opinions and on key questions:

- What is "similar enough"? What clinical trials will be required, if any? How do you deal with immunogenicity, and what will be required for efficacy and safety? "A lot has not been prescribed in the legislation, it's going to be up to the FDA to define that pathway," says Hudes.
- If you are going to have a cost of clinical trials and biologics manufacturing capability, what is really the economic impact going to be of an generic? Is it going to reduce the cost by 20% or 50%?
- Who is going to get into biosimilars? Large biopharma? Specialist companies in India or China? "Right now there is a lot of activity, but I think the economics will come into play because it's not cheap to create a good biologics capability and the regulatory aspects that go with it. It is truly a disruptive innovation. We don't know who is going to emerge, but it's going to be the one who has a real core expertise in biologics."
- What are the legislative implications and their effect on innovation? "Some folks feel that the legislation didn't create an immediate pathway to products on the market. I think it's an important first step. We're going to see more legislative changes and practical changes as FDA starts to get into that area. My big concern is the unintended consequences, not only of legislation but also of the pathway that gets created. It would be very possible to disrupt or lose the US biopharmaceutical industry's global leadership if we don't watch carefully what we're doing. You can easily kill innovation if the wrong steps are taken in this area."
- What are companies doing to stay profitable? "Two years ago, I asked one industry executive, 'What is your strategy for dealing with the threat of biosimilars (this is a company that had a number of products that looked like they had some challenges)?' His response was 'We're going to innovate our way out of this.'"

Efficiency Is a Priority

"Fail early, fail often" may be the mantra for efficiency in the biopharmaceutical industry, but, says Hudes, until now "it's been words only." The real change hasn't come, he says, because it hasn't been a priority. "But I believe it will be. The whole area of process science will play a big role in efficiency and improving yields. Improving the process has two effects: one is that by really characterizing and understanding the process, you are able to make process improvement and make changes rather than follow whatever process is put in place. You have more incentive now to refine that process. The other aspect is that as you understand the process better, you can also use that opportunity to protect your intellectually property that is under attack by biosimilars" (see box on this page).

Healthcare Reform is also driving the need for greater process efficiency. According to Hudes, the "big picture" in healthcare reform is that volume will increase to serve the additional 32 million people who will be covered, which means the market for life sciences is larger. Because the government will be the largest payer in the whole landscape, the price of pharmaceuticals in general will decrease. "So if you have the simple equation of volume going up and price going down, then the only way out is to be more efficient. You can't just put more innovative products in the pipeline if your margin is going to go down, you may even lose money. And you can't lose a dollar on every dose and make it up in volume, it just doesn't work," says Hudes.

The result is that operational efficiency becomes a higher priority, including manufacturing, supply chain, sales and marketing, and clinical development. "We are not going to see it immediately because healthcare reform rolls out between now and 2020, but during that journey I believe the topic of efficiency will become a priority."

Cost-Saving Technologies

Traditionally, manufacturers have placed a higher priority on the costs of research and development over those for manufacturing, and the cost of goods sold hasn't been their biggest concern. However, as pricing and margins decrease, managing manufacturing costs and efficiency becomes more important. As Hudes observes, this means there should be more funding for manufacturing efficiency improvement — including a more important role for technology in helping reduce costs — and there will be more willingness to tweak the process to get more out of it. "Flexibility in control systems becomes more important because you know you're not going to just release the process and never change it. You're more likely to want to continuously improve that process, even if it means additional submissions," says Hudes. The current widespread use of technologies such as single-use systems, platform technologies, and streamlined expression systems already reflect this trend.

Single-Use Systems: Certainly single-use systems are the technology of greatest interest. The advantages of their implementation, including energy savings, have been discussed elsewhere, including in this issue. For local manufacturers, (except those at large-scale production, where the use of stainless steel may be more efficient, as mentioned in the article by Andrew Sinclair in this issue), single-use systems lower installation costs. Operation costs are also less because disposables help shorten time to build in accordance with regulatory requirements as well as shorten changeover between processes.

"Disposables allow a company to implement a process with far less capital investment," says Ransohoff. "Companies are looking at what the hurdles are to getting a process up and running in a local geography. One is capital investment, and the other is technical expertise. Disposables help in both of those areas."

Modular Units implementing single-use systems also could bring real value for setting up local manufacturing. Leveraging single-use and modular technologies has been a way of building flexible platforms. "We often find it is important to build flexibility into your facility. If you're looking at simply making an existing molecule somewhere else, flexibility is not as much of an issue. But if you're thinking about decentralizing your global manufacturing supply chain, you're probably going to want to make more than one molecule at each location. So the technologies allowing flexibility to make this happen are particularly interesting," says Peter Latham, cofounder and president of BioPharm Services US.

Simplified Upstream Systems shorten process time and, depending on the protein and demands of the system, may reduce overall costs for manufacturers in emerging markets. Such systems include the *Pf*ēnex Expression Technology based on *Pseudomonas fluorescens* (www.pfenex.com); Selexis SURE Chinese hamster ovary (CHO)–based cell line development (www.selexis.com); Ajinomoto's Corynex system based on the *Corynebacterium glutamicum* genome (www.corynex.com); and CMC Biologics' CHEF1 mammalian and *Escherichia coli* systems.

Platform Technologies are baseline systems that allow a company to bring a product through manufacture by implementing similar process steps for all products (e.g., antibodies). For a certain pipeline of products, a platform consists of the same host cell line, the same expression vector, and the same manufacturing process (with minor modifications depending on the product being expressed by the cell).

"The more common denominators you can keep in your platform, the more you can use past experience to minimize the amount of process development required," says Susan Dexter, principal consultant, Biopharm Services US. "When expressing antibodies in the same expression vector, using the same host cell line and same purification process steps, then it's more of a product specific optimization process. There will always be differences between proteins being expressed, but with a platform, you take advantage of the well-characterized parameters."

During *BioProcess International*'s presentations at Interphex this year, Jim Wilkins, chief technology officer at Sensorin, said that the current move to platform purification technologies is taking place mostly at large companies, which are working to develop monoclonal antibody processes that are more uniform. "These defined technologies then enable local manufacture through greater understanding of the potential process issues. So as we understand the protein molecules that we're working with better, we're going to be able to define the purification strategies that we use."

Laureate Pharma is a contract manufacturing organization (CMO) that focuses on recombinant proteins made by mammalian cells to 2,000 L scale. According to Ultee, the company uses platform technologies. It has a defined set of procedures applied to a cell line or its product (the antibody, typically), which is made by the cell, and processing is conducted under a similar pattern (platform). Using a platform is especially efficient for monoclonal antibodies, the dominant molecule in biopharmaceuticals. "You can't use a platform procedure if you have a unique molecule. It has to be one of a class of molecules and a platform applies generally to members of a class, the one most common being the IgG antibodies," says Ultee.

The most common method is to use a platform that involves an initial capture purification on protein A, which selectively binds on IgG antibodies and nothing else. Then there are usually two "polishing" steps to remove trace amounts of host cell proteins, DNA, and provide additional viral clearance. With CHO cells, for example, you can base a platform technology on the kind of media you're going to use and the feed you're going to use. "You know in general what a good medium might be for a certain parental CHO cell; it may not be the perfect medium, but you know you can grow it," says Ultee. "You could then have a upstream or bioreactor platform as well as a purification platform."

Another BPI speaker at Interphex was Rahul Singhvi, CEO at Novavax, who presented a case study of how his company used a platform technology for producing a pandemic influenza vaccine based on virus-like particles. The company used a recombinant technology in which some of the genes of the virus are coexpressed, come together, and self assemble themselves into a particle that looks like the influenza virus. They mimic exactly the influence of particles, except that they don't contain the genetic materials required for application of the particle. The particles can then be "redecorated" with antigens of influenza or other diseases, thereby forming a platform for a SARS (severe acute respiratory syndrome) or HIV (human immunodeficiency virus) vaccine candidate.

"So with the same manufacturing process, just by manipulating the genes, I can make different type of antigens," said Singhvi. "Most of the equipment that we use is simple equipment that is ready to use, [including] gamma-radiated bags or liners and generally low mechanical energy based purification systems."

Even when local manufacturing in an emerging market makes economic sense, it is not without some level of risk and complexity. To minimize these risks and increase operational efficiency, forward-thinking companies are taking advantage of single-use systems, streamlined expression programs, and platform technologies for targeting specific localized diseases (e.g., SARS, Hong Kong flu), setting up closer to where these diseases are, and being aware of market changes attributable to social and legislative decisions.

References

1 Kaplan W, Laing, R. *HNP Discussion Paper: Local Production of Pharmaceuticals: Industry Policy and Access to Medicine* (The International Bank for Reconstruction and Development/The World Bank, Washington, DC, 2005).

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