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Reaching for Next Gen Biopharma Manufacturing

by: Rebecca Stauffer, PDA | Mar 07, 2017

Robotic arms. Gloveless isolators. Manufacturing pods. Process modeling. Big data. Automation. Welcome to the future—or "next generation"—of pharmaceutical manufacturing, "Industry 4.0." Pharmaceutical manufacturing is on the precipice of a paradigm change, particularly when it comes to biologic products. As biologic lots become more and more specific, some even personalized for individual patients, the need for flexible, high-tech manufacturing equipment and solutions becomes critical.

Yet when a biologics manufacturer decides to employ these next generation technologies, serious practical considerations emerge around finances, training, and implementation. **Barry Starkman,** Principal Consultant, Parenteral Manufacturing, DPS Engineering, and **Mike Vandiver,** Vice President, Manufacturing and Plant Design, Just Biotherapeutics, are both well aware of the heavy decisions involved in putting these new technologies to work. They will share their experiences at the *2017 PDA Annual Meeting* (Plenary 3: "Next Generation Manufacturing & Facilities," April 4, 8:30 a.m.).

In theory, next generation manufacturing should require less capital investment than conventional facilities. Still, cost does factor in when installing and implementing new technologies. Yet some companies have found ways to successfully manage these expenses.

"I think that the big issue is around investment," explained Starkman. "The cost for putting in a filling line, once you've made the decision to do that, is pretty steep." For this reason, he explained, some biologics manufacturers are using their clinical manufacturing facilities to launch. This enables the company to gauge how well the product performs on the market before committing to invest in flexible manufacturing technology.

Vandiver believes that the production of innovative biologics necessitates flexible manufacturing.

"In the past, to very successfully supply the world with biotherapeutics required a huge investment and substantial fixed assets," he said, adding, "in the future, the primary characteristic of next generation biologics manufacturing is flexibility. The key tenets supporting flexibility are speed and cost-effectiveness."

Starkman, who handles the conceptual design of facilities for DPS Engineering's clients, also pointed out that companies that have invested significantly in the research and development of a new biologic product may be gun-shy about taking the risk when there are major obstacles to overcome in getting the product on the market in a timely manner. Particularly when one of those hurdles is fitting next generation manufacturing technologies in with existing regulations.

"At some level, as you're moving technology [ahead], somebody has to be first, and then you run the risk of a regulator either not understanding or not agreeing," he said. "And when you have large sums of money on the line, both in terms of investment and in research and development as well as the capital equipment…it becomes quite easy to say 'you know, let's just go with what we know.'

"That's a very difficult decision for the owner to make, to go forward with something totally new. I'm not sure how to overcome that in total. Other than the fact that more work may need to be done with prototypical process design."

In addition, Vandiver noted that certain products may be produced using legacy systems for a variety of reasons. Moving existing products to new production technologies would require a large investment in clinical trials to establish comparability, something many companies may not be able to do.

"When you look at these [legacy] systems, people have invested hundreds of millions of dollars in a facility such as this. And for them, it may not necessarily make sense to invest in one of these other types of facilities," he said. "They made such a large investment; they want to make sure it's fully depreciated. And, if I were in their shoes, I would believe the same thing."

Maik Jornitz, CEO, G-Con Manufacturing, and moderator of the Annual Meeting session featuring Starkman and Vandiver, sees the key performance factors behind next generation manufacturing as flexibility, speed and cost.

"Flexibility is required to be able to act rapidly on changing environments, but also to be able to manufacture multiple products within the same facility. Speed, another key aspect, means the time-to-run frame needs to be lowered to less than a year instead of the [current] three to four years," he said. "Cost, the third element, should be [seen] as total cost of ownership and not in the legacy approach of cost per square foot."

Just Biotherapeutics is designing and building a small, efficient biologics manufacturing facility, named "J.Pod," that Vandiver believes will drive down capital investment and the cost of goods. He sees J.Pod as complementary to existing conventional production facilities.

"I want to be very clear. I am not actually advocating that these new types of flexible facilities actually replace conventional facilities," he emphasized. "I believe they complement existing conventional production facilities," explaining that, if you need multimetric tons of product, it would not make sense to invest in a J.Pod facility. But it would be suitable for moderate-scale production, up to a metric ton.

Just Biotherapeutics starts by using modeling of the process technologies under consideration in order to identify bottlenecks and prioritize technologies on which to focus attention.

"We actually use modeling first," Vandiver explained. "We start by modeling mass throughput and investigating options. We then model the economics around these options, in terms of cost of goods." This allows his company to determine the impact of volumetric productivity and its role in reducing the cost of goods.

“Let’s just say that my initial market only requires two bioreactors. Based on the volumetric productivities, our cost per gram is potentially going to be something around $100–$150 a gram. As we then require more capacity, our markets increase, our demands increase. We can increase to four to six bioreactors very quickly and very cost-effectively. And we actually see the potential to lower the cost per gram to the $40–$60 range, so what we’re seeing, then, is about a three-fold reduction in the cost of goods.”

Yet, while the regulatory concerns of migrating to new technologies remain, both Starkman and Vandiver stressed that regulatory agencies, such as the US FDA, understand the need for innovative manufacturing technologies.

“I think there’s been a step change,” Starkman said. “There is more of an openness.”

From what he’s seen with his clients, the key to receiving regulatory approval when implementing new technologies lies in truly understanding the manufacturing processes of the new equipment and effectively communicating this to regulators. Risk assessments, in particular, have proven to be an effective tool.

“Certainly, FDA has moved toward new technologies as an organization because they see the value in it. It’s still in its early stages but I think it’s in the right direction, for sure,” Starkman said.

Vandiver agrees that the Agency is supporting new technologies, especially disposable technologies, which are becoming the standard in the industry over stainless steel.

In fact, he pointed to a recent survey from *BioPharma-Reporter* showing that “70% of the respondents actually agree that disposable technologies are becoming standard, and it shows that the regulatory agencies are supporting this as well.”

New Training for New Tech

When a biologics manufacturer makes the decision to implement next generation technologies, training is just as critical, if not more so, as it is when implementing conventional equipment.

Starkman explained that training becomes particularly pertinent when working with automation, which requires a different level of understanding. A worker on the production line must understand “how it feels to control the equipment, [as] the days of just being able to turn a wrench and being able to set up a machine like that are somewhat diminished.”

With these new technologies, operators are responsible not just for running it, but for setup, preventative maintenance and understanding how it operates. Vendors do a “great job” of designing the equipment and developing innovative improvements. Yet at the end of the day, “they don’t stay and run the machine; they disappear after the machine is on the floor producing every day.”

When building a line, DPS Engineering brings the workers who will be responsible for the line into the design process, including taking operators to specialized training at a site in Germany. This ensures the workers understand upfront how the machine works, moving up the learning curve, and fostering commitment on both sides.

“You need to have that kind of commitment in the parenteral drug business because the criticality of what we’re doing is so important,” Starkman explained. “Building that relationship among all the parties involved is very important, and it starts at the very beginning.”

Just Biotherapeutics will also develop internal training programs to prepare the staff, mitigating risk.

“We are creating internal training programs that bring people up to speed and prepare them for these new types of operations,” he said. His company approaches it more as expanding skill sets rather than replacing old ones. This makes the employees more flexible, enabling them to work in different types of facilities—a highly desirable trait.

And Vandiver has found that Just’s staff is receptive to learning to work with new types of equipment. “For them, it’s exciting; it’s new. They’re not doing the same thing that they’ve done for the past 10 or 15 years,” he said. “They’re being exposed to new ways of doing things. They have actually embraced the change.”

Starkman agrees that workers have generally been receptive to learning new skills. “I think that people love the technology. They love the sophistication of it. They love the ability to learn new things.”

And while operator skill sets are changing, one thing is staying the same: the human element. At least for the time being.

In his personal time, Starkman is a pilot and enjoys flying. He finds aerospace automation analogous to biotech automation.

“Flying airplanes years ago was a very ‘seat-of-the-pants’ type of operation. You flew an airplane by feel…today’s airplanes are very automated. Everything is digital,” he said. “There is a tendency for pilots to get overly reliant on the automation of the airplane—to just let it go—and they’re not paying attention. There have been a number of serious situations that have occurred as a result.”

To prevent overreliance on automation, Starkman recommends better understanding of the manufacturing process itself. This builds an “envelope” of understanding.

“We can build in controls with the right sensors,” he said, and by “understanding the process, understanding the risks of the process very well, the machine can, in effect, monitor itself at some levels better than a human can. But I don’t think you will ever get away from [a human presence] in such a critical scenario like making parenteral drugs. I think the human factor is always going to be there.”

In the end, no matter what types of next-generation manufacturing technologies are implemented, multiple factors need be taken into consideration. Such firms might consider taking into account the specific needs of the product and the market demands.

Jornitz urges companies to look into next generation manufacturing to avoid being left behind.

“The early adopters are already out front,” he said. “The most radical change that has to happen is in the attitude and thought process within the industry.”

About the Experts

Barry Starkman has amassed over 30 years of experience in biopharmaceutical facility design and operation.

Michael Vandiver is Vice President, Manufacturing and Plant Design at Just Biotherapeutics. He has over 29 years of biopharmaceutical process development and manufacturing experience.

Maik Jornitz is a distinguished technical expert with close to 30 years of experience in bioprocesses.

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