FUTURE FACTORIES FOR MANUFACTURING FLEXIBILITY

Scott Fotheringham, PhD

In the 1970s, Nucor, which had been a nuclear energy company, decided to pivot vertically into steel manufacturing. It transformed traditional production, lowering costs by using scrap metal and electric arc furnaces instead of the more expensive iron ore and blast furnaces on which companies like Bethlehem Steel relied. Nucor was so successful at capturing the lower end of the steel market, making rebar and other low-quality steel products with its mini-mills, that it disrupted the integrated steel mill industry. It eventually became the largest steel producer in the US.[1]

Disruptive Innovation

This example of disruptive innovation—the term coined by Clayton Christensen in *The Innovator's Dilemma* (1997)—serves as inspiration for the thinking and planning of John Cox, Executive Vice President of Pharmaceutical Operations and Technology at Biogen.

"I look at other industries, like steel, that have made huge shifts in their manufacturing processes," Cox says. "They went from batch mode to continuous mode, from large plants to mini-mills. The companies that embraced these innovations put themselves in a strategic position. I think the time is ripe for this type of disruptive innovation in bioprocessing."

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Cox is asking how pharmaceutical manufacturing, which is driven by capacity constraints, existing and to-be-built pipelines and the risks of sinking capital into future projects, can embrace innovations to provide the mass of drug product required by the booming market for monoclonal antibodies (mAb) and other biologics. It's a classic dilemma.

"Should our process engineers continue to improve technology's so-called sustaining innovations or, instead, as mini-mills did for Nucor, should we be investing in smaller, more flexible and agile technologies as we aim to meet market demand?" he asks. "We're at that kind of pivot point in our industry and Biogen is placing significant bets and investments around these new technologies to be ready for the future."

John Cox, Executive Vice President of Pharmaceutical Operations and Technology at Biogen.

Cox wants to see a new dominant design in pharmaceutical manufacturing, one that will come about through collaboration between academics, suppliers and industry engineers. He embraces a hybrid model of factory design, one that combines the flexibility and lower capital investment of portable, disposable systems with the high volume and throughput of stainless steel, to ensure production that will meet the needs of the types of patients that are the focus of R&D at Biogen. There is a need to improve production processing, particularly for biopharmaceuticals aimed at diseases such as Alzheimer's and multiple sclerosis (MS), so Biogen can supply the demand for metric tons of product annually.

"It's this scale of capacity capability from a single plant that will enable the products that this industry is embracing in biologics," he says. "Whether it's the cancer therapies (e.g., PD-1s), the PCSK9s or the Alzheimer's drugs that we and others are working on, we need this improved production.

"Right now there's a need to transform the throughput of large-scale plants to meet this demand. Our task is to figure out how to move from large-scale plants capable of producing kilogram quantities of product to ones capable of producing 10 tons of product annually."

The Evolution of Manufacturing Technologies

Cox points out that, since 1980, pharmaceutical product titers have followed a variation of Moore's Law, which holds that the number of transistors in an integrated circuit doubles every two years. Titers have increased 1000-fold from their levels in 1980 (0.01 g/L) with facilities now routinely hitting 10 g/L. While these increases are substantial, what is equally impressive is that the price per gram of product has fallen 200-fold in the past 35 years to a mere $50. Advancements in downstream processing have taken advantage of these high titers to bring about process yields of 3 g/L and more.

This rapid improvement in drug substance output has come about through an evolution of manufacturing technologies and factory design. These include the introduction of large-scale (20 kL) bioreactors and six-pack plants; the portable and ballroom concepts of design; single-use technologies to complement the traditional, fixed, stainless steel equipment; emerging contract manufacturers; and bioprocessing. Culture and purification improvements include significant increases in titers through high-titer yielding expression vectors, better parental cell lines and cell culturing (e.g., N-1 perfusion during seed train[4]), high-capacity purification and single-pass tangential flow filtration.

Simultaneously with these innovations, cost-cutting and streamlining saw the industry transform from one characterized by internal and domestic production, low utilization (an average of 54 percent) and significant inventories into one with outsourcing, global production, low inventories and high-capacity production. The accompanying quality issues and drug shortages that became common were, and continue to be, a concern. However, the good news is that pharmaceutical earnings are up almost 60 percent since 1990 and the pharmaceutical industry is expected to reach $1 trillion in sales by 2020. This new era is characterized by the burgeoning biologics sector, fed in large part by the market for large molecules (especially immune-oncology products), biosimilars, emerging markets and targeted niche drugs.

The Need for Production of Metric Tons While Maintaining Quality and Supply

Cox sees this transformational time for the industry as replete with challenges for people in operations, manufacturing and supply, particularly to meet this need for metric tons of product. While the dosages for Biogen's high-potency products like Avonex®, an interferon used for the treatment of MS, are in micrograms, dosages of mAbs tend to be in the range of milligrams. Couple this with the large, and growing, populations of patients with MS, Alzheimer's and various cancers and it is obvious why Cox is focused on the need for increased throughput.

"The industry is faced with the opportunity to think about capacity very differently," says Cox. "We're not treating handfuls of patients, or orphan drug numbers of patients, but millions of patients."

Biogen has 18 biopharmaceutical experimental therapeutics at various phases of clinical trials, including Daclizumab High-Yield Process, developed in collaboration with AbbVie Biotherapeutics, which has been filed with the FDA. It is for patients with relapsing-remitting MS. Aducanumab (BIIB037) is a monoclonal aimed at reducing amyloid plaques in Alzheimer's, which showed positive Phase 1-b trial results last March. Phase 2 results were disappointing, especially for the mid-range dose[5], but a Phase 3 trial has begun, with 1,350 patients for the five-year study. Anti-LINGO-1 (BIIB033) is in Phase 2 trials as an experimental re-myelinating mAb for MS patients.

A further factor influencing the need for metric tons of product is the need for high dosages to breech the blood-brain barrier for neurology products such as a mAb targeting amyloid plaques in Alzheimer's—higher doses are needed because a low percentage of the drug actually makes it to the brain.

The Question of Capacity

"There is a capacity need across the industry right now, not just for monoclonals, but for all large molecules, including recombinant and fusion proteins," Cox says. "Fortunately, the doubling of productivity that we've seen every few years applies to these products as well."

The launch volume of a drug product that the market requires depends on dosage, the number of potential patients and the production titer. As Andy Skibo points out elsewhere in this issue, launch volumes are difficult to predict and may vary by a factor of as much as 17.

This uncertainty when launching a new product means that companies need a flexible supply chain that can respond quickly to a wide range of possible production amounts. Until the required dosage of an experimental drug is identified and the production process (e.g., titer and production yield) is worked out, it is difficult to estimate the needed capacity.

"The way people have dealt with demand uncertainty is to build massive amounts of excess capacity," Cox says. "We went with massive amounts of stainless steel and, because of the uncertainty of both demand and the pipelines, we had significant

Biogen, with headquarters in Cambridge, Massachusetts, discovers, develops, manufactures and markets treatments for neurological, haematological and autoimmune diseases. It had revenues in 2014 of $9.7 billion.[2]

Its products on the market include the recombinant fusion proteins for hemophilia, ALPROLIX™ and ELOCTATE™. For relapsing forms of MS, there are two interferon products, AVONEX® and PLEGRIDY®, as well as TECFIDERA, the number one prescribed oral MS therapy in the U.S. More than 135,000 MS patients have been treated with TECFIDERA worldwide as of 2014. Monoclonal antibody products include GAZYVA®, indicated for chronic lymphocytic leukemia, which was the first product approved by the Food and Drug Administration (FDA) as a breakthrough therapy, and RITUXAN®, which is indicated for non-Hodgkin's lymphoma. These anti-CD20 mAbs are commercialized in collaboration with Genentech (Roche), earning Biogen $1.2 billion in revenues last year.

Biogen, like all of the industry, is adjusting to recent developments in pharmaceutical manufacturing[3] that include the globalization of markets and of production, patent expirations of blockbusters and the concomitant introductions of biosimilars and the design, development and testing of biopharmaceuticals targeted at specific diseases. These latter, breakthrough products, while promising to be incredibly valuable to the industry—not to mention to patients—bring up challenges for the industry, notably the need to increase factory output.

under-utilization across the industry. Then there'd be times when suddenly there'd be shortages because we hadn't built in advance and there'd be overbuilding. When capacity is not being used there are billions of dollars not being used. We ought to think of those billions in excess capacity as money that could be used in the healthcare system for more clinical trials."

On the other hand, when capacity is needed, a large-scale plant today can cost roughly $1 billion and take five years to design, build and license by the agencies for commercial product. Companies taking huge capital risks long before they know the product is going to get approved characterize the industry.

"You can't start building the plant after you have phase 3 results or else you'll be waiting two or three years to produce it," Cox says. "You have to take a huge risk and build rigid infrastructure, burying a large amount of investment capital in the ground."

Then, if the company finds out it needs four or eight or 17 times the amount of product, it simply won't be able to build the plants in time. Adding to the complexity of planning is the FDA fast-track approval process[6], especially for experimental drugs that might save lives of late-stage cancer patients, which can see a break-through product pass from Phase 1 to Phase 3 in a year.

"It's rare in this business for a plant to manufacture the product for which it was originally built," Cox says. "You have such un-certainty, at least historically, that it's incumbent on the people in supply and manufacturing to figure out how to reduce that capital risk investment while at the same time ensure supply certainty particularly for the kind of diseases we work with."

Designing plants and processes to be as efficient and nimble as possible can mitigate demand uncertainty.

"Using process sciences combined with process engineering capabilities has permitted our industry to respond to this type of demand uncertainty. For example, academics and some companies are starting to work more with continuous processing, using innovations like N-1 perfusion cell culture upstream. Also, if we can increase the productivity of a cell line four-fold through process science, the impact on our capital investment and our responsiveness would be enormous.

"These new technologies could disrupt manufacturing. We're doing the basic engineering research on this now because, in five years, we want to see these technologies in place. For those of us working in the engineering side of the business, we ought to be thinking and working as hard as we can to implement these technologies, processes and capabilities to be able to use capacity efficiently and get the maximum output."

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GETTING INNOVATIVE, QUALITY MEDICINE TO PATIENTS, WHEREVER IT'S NEEDED

Lee Spach, Director, Global Supply Chain Hemophilia Franchise Lead and Adam Sherman, Director, Program Leadership and Management, Biogen

Lessons learned from building a large-scale humanitarian aid infrastructure to securely and reliably deliver medicine to some of the world's poorest countries

A year ago, Biogen and Swedish Orphan Biovitrum (Sobi) set out to make good on a promise – produce 1 billion international units (IUs) of hemophilia clotting factor for humanitarian aid purposes, the largest donation of its kind. The first 500 million IUs of the donation will be distributed by the World Federation of Hemophilia (WFH) over five years as part of their Humanitarian Aid program.

This fall, the WFH will deliver the first shipments to clinics in developing countries around the world, including, Senegal, Ghana and the Dominican Republic. Treatment centers are used to receiving donations on an unpredictable, ad-hoc basis. Now, these clinics will receive a predictable, steady supply of medicine. This not only expands patients' access to potentially life-saving hemophilia treatment, it creates a sustainable hu-manitarian aid model that can change the way hemophilia is treated in these countries.

However, achieving our goal has not been easy. A donation of this scale and scope hasn't been attempted before, largely because the infrastructure to manufacture, securely and reliably deliver, and distribute therapy in countries of need did not exist.

Assessing and Addressing the Challenge

When we began this journey, we immediately identified several challenges.

Commercial pharmaceutical distribution channels are highly regulated and clearly defined. But humanitarian aid channels are not. The medicines donated through humanitarian aid programs are often not approved for commercial sale in a country receiving the donation and may require additional importation steps. The complexity of production and delivery to patients through non-commercial channels is enormous, with each country presenting unique nuances, processes and requirements.

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Cox believes that, moving forward, it won't be about who has the most stainless steel. Historically, companies have made decisions based on titers and calculated the number of liters of bioreactors they would need to meet the projected launch volumes.

"For years the idea was to get higher and higher titers," he says. "But the size of bioreactors and cell culture titers doesn't get at the real manufacturing objective, which is manufacturing throughput. The challenge for our process engineers has moved from getting high titers in these large bioreactors to how to process this much material. Our challenge has moved from one of production to one of purification."

Which circles back to the original question Cox posed: How are companies going to produce metric tons of biopharmaceuticals to meet demand?

Biogen's Future Factory Design—Flexibility in Manufacturing

Biogen's philosophy is that drug substance biologic manufacturing, scale up, technology transfers, managing redundancy and supply risk should be core competencies of the company.

""There are some others who don't consider these core competencies and they contract work out, but we like to do all this internally," says Cox. "We intend to stay at the forefront of this."

Cox understands that there may be times when a company underestimates the amount of product that is needed and has to go to a contract manufacturer. Meanwhile, CMOs are increasing their capacity right now, trying to respond to the demand for biologics. However, he prefers to reap the benefits of keeping internal control of supply and production.

"Take our work in Alzheimer's with Aducanumab®, and other products in our pipeline," he says. "These internal core competencies allow us to rapidly design and build a plant that will fit with the process science and engineering that we apply for that product. As a consequence we don't need to fit our processes into a contractor's facility. This puts us in a better position for launching a product. That way we maintain control of our destiny with a product that's significant for Biogen's future."

The result of this planning is multiple plants where Biogen engineers know they can run any number of the company's products using common platforms.

"We can validate and qualify them in each of our facilities. We can keep this redundancy and we can move products around to maximize utilization."

At the same time, Cox is aware of the risks that manufacturers open themselves up to in terms of quality and supply by aiming for this high capacity utilization.

"I know that groups like the ISPE are looking at how we change manufacturing, regulatory and quality to keep improving," he says. "There has to be a willingness in the industry to work with the FDA and other agencies on these new technologies to elevate quality, efficiencies and throughput. We take a hard look at how we follow and validate products, ensuring quality by using new tech in quality metrics and analytics."

The new factory model that Biogen is betting on is a hybrid dominant design that leverages a mixture of its existing plants and what it calls future factories. The latter, using disposable tanks and single-use purification, reduce cycle time, are portable and are cost-effective for small, clinical quantities of product. They are meant for early-phase production while allowing an increase in scale to meet demand variability. These are combined with stainless steel systems that are cost-effective for high volumes and throughput, have relatively low variable costs and represent sunk costs for many companies. Biogen combines its 2 kL bioreactors for high titer late-stage clinical and commercial production with its 15 kL bioreactors, on which it relies for high-demand products.

"There's a lot of debate in the industry about using disposables versus stainless steel," Cox says. "In terms of economics, it makes sense to use disposable for early stages of development, where you want to make a small amount of product to bring it through R&D to proof of concept. This gives us speed, is not a massive amount of capital investment and keeps us at the forefront of those technologies. It's an inexpensive way and means we aren't tying up a stainless steel plant to do it. Our plan for the production of monoclonals that are needed to supply large numbers of patients remains large-scale stainless steel.

"We still have to be investing in capacity, using disposable as well as building new stainless steel but, instead of building two or four new plants, we're going to build a plant that has a step change in terms of productivity. We then have a choice of being able to go rapidly from low to high utilization, depending on what's needed."

Biogen has plans to build another plant in Switzerland within three to five years that will maximize throughput up to five-fold compared to what a plant that size has produced historically. The new facility will incorporate Biogen's re-designed manufacturing, still focused around stainless steel and large-scale bioreactors, but rebalanced upstream and downstream with new technologies and equipment to improve productivity to the point where it will meet the goal of manufacturing metric tons of product annually.

"If we want to provide drugs to patients around the world, we have to have this capacity increase," he says. "It's extremely expensive to produce these biologics."

Cox see benefits of this hybrid-dominant design of plant beyond the bottom line. The capacity improvement and throughput capability of the company's plants leads to reduced costs, which in turn has allowed Biogen to announce a humanitarian aid donation program for hemophilia.

"It comes down to manufacturing, capacity, technology and our technical development capability that makes this kind of aid possible," Cox says. "We have a credo at Biogen: Caring deeply, working fearlessly and changing lives. All three are important and what we're doing with manufacturing will continue to help us live up to this credo."

John Cox knows he has to stay on his toes.

"Beyond the next five years, if our industry continues to move in this direction, the question I have for process engineers is, what's next?" ◂

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