





Plantopia?

A mandate for innovation in pharma manufacturing

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Change is badly needed in pharma manufacturing. Now that the “blockbuster” model of excess capacity has run its course, it’s time to move toward operations excellence—a model marked by smaller batches, shorter runs, greater quality expectations, and further innovation in production itself. In short, pharma leaders now need to look beyond simply running manufacturing efficiently. They must challenge their operations leaders to say what they plan to do differently going forward.

If engineers who had worked on a manufacturing system for an automotive company in the 1950s were to visit a state-of-the-art automotive plant today, they would be astonished by the many changes.

They would immediately notice the robots tirelessly spot-welding car bodies where men in welding masks once worked. They would observe the fast-changeover paint booths that help each production facility to meet the vagaries of market demand. They would be intrigued by how the just-in-time parts delivery systems function so well. And they would most certainly be surprised by how much total value of each car is outsourced to suppliers.

Their counterparts in the steel industry would experience a similar study in contrasts. Today's mini-mills are economical at a tenth of the scale of large integrated mills. They can turn operations on and off to match production runs to market demand, and need 60 percent less energy to run as compared to traditional mills.

However, there are few such stories in the pharmaceutical industry. The short story is that other industries have pushed manufacturing innovation far and fast, but pharma has not. And while others have innovated in collaboration with their networks of suppliers, that has not been the case with pharma.

Pharma's manufacturing economics have not changed much in the last few decades; gains in pharma production have been modest, marked by the recent use of lean production techniques to cut variable costs and boost labor productivity. Yet, little attention has been paid to overall asset productivity, beyond the usual rationalization of production sites prompted by overcapacity. Manufacturers have squeezed some gains out of the shop floor, but have not yet applied the same thinking to the design and engineering of their assets.

In a 2004 report, the US Food and Drug Administration put it this way: "Pharmaceutical manufacturing operations are inefficient and costly. Compared to other industrial sectors, the rate of introduction of modern engineering process design principles, new measurement and control technologies, and knowledge management systems is low. Opportunities for improving efficiency and quality assurance...are not generally well recognized."¹

Little has changed since that report was published. Yes, there are exceptions: Novartis, for example, is making the right kind of efforts by working with the Massachusetts Institute of Technology to co-develop its future manufacturing capabilities.² Other companies are piloting continuous process tablet lines. But the great majority of efforts have focused on the near-term cost-reduction levers of labor and procurement.

Fundamental changes in how products are made, and in how quality is built in rather than tested in, remain few and far between. Continuous batch manufacturing and biologics production in disposable reactors remain niche activities. On-line process analytical technology (PAT) and the use of control limits, common for more than 20 years in the automotive sector, are rarely seen. Quality by design (QbD) practices are still nowhere near mainstream.³ Even the presence of a U-shaped packaging line or work cell to optimize

1 *Innovation and Continuous Improvement in Pharmaceutical Manufacturing, US Food and Drug Administration, 2004.*

2 "Novartis-MIT Center for Continuous Manufacturing," MIT Engineering Web site; "MIT and Novartis in New Partnership Aimed at Transforming Pharmaceutical Manufacturing," MIT press release, September 28, 2007; "With Continuous Operations, Can Drug Manufacturing Become a Rock Star?," PharmaQBD, November 2010.

3 Agnes Shanley and Paul Thomas, "Flexible Pharma: Puzzling Out the Plant of the Future," *PharmaManufacturing.com*, 2009.

labor use, common in consumer goods, is not standard in most fill and finish plants. Nor is it part of the typical products offered by pharma equipment manufacturers.

It's time to elevate manufacturing innovation as a strategic priority. The earlier paradigm of pharma operations—typified by the blockbuster model—is being replaced by shorter periods of exclusivity, higher complexity, smaller batches, competition based on product efficacy, less productive R&D pipelines, more price transparency, and greater purchaser power.

Yesterday's choices—prioritizing product launch timeliness over process stability, reserving enormous excess capacity, and choosing safe and conservative technologies—are not right for today. Today, pharma operations leaders must rethink their approach to manufacturing and demand more innovation that matches the already changed pharmaceutical landscape.

Leaders cannot look at their next manufacturing asset and declare, as one company executive did, that “we are building a museum on our next site.” In short, they must conceive of and plan for what we might call “Plantopia”—that is, the future production scenarios that represent possible and practical responses to the challenges ahead. Before dreaming of the future plant, however, we must understand the forces driving this change.

A strong case for step change in manufacturing

Innovation hasn't happened in pharma production before because it hasn't been necessary. But times have changed. The opportunity cost alone makes an urgent case for innovation. Some estimates put the potential worldwide cost savings from efficiency improvement as high as \$50 billion⁴—equivalent to the cost of developing 80 to 90 new drugs every year.⁵

Our longtime studies across a wide range of industries point to five broad sources that propel innovation. To begin with, **global forces** are challenging the old paradigm. Gone are the days when pharmaceutical operations could rely on the US, Japanese, and European markets. Emerging markets will represent about 45 percent of the world's GDP by 2018 and are expected to grow twice as fast as developed markets between 2008 and 2018.⁶ And yesterday's stable regulatory environment is being reshaped by other nations' regulatory bodies with different standards and expectations, shorter periods of

4 Philipp Cremer, Martin Losch, and Ulf Schrader, “Driving a Transformation in Efficiency,” *Outpacing Change in Pharma Operations*, McKinsey, 2010.

5 *Innovation and Continuous Improvement in Pharmaceutical Manufacturing*, US Food and Drug Administration, 2004.

6 *Global Insight's World Overview*, McKinsey analysis.

exclusivity, and rising quality expectations. One analysis shows that exclusivity for blockbuster drugs has dropped from 13.8 years to 11.2 years.⁷

Another driver involves **changing customer needs** in terms of both price and drug efficacy. Prices must be far lower if pharmas are to successfully serve the “next billion” consumers. Recently, the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunizations, a global health partnership launched in 2000 to increase access to immunizations in poor countries) revealed the prices paid for vaccines, prompting both GlaxoSmithKline and Merck to significantly reduce the costs of their rotavirus vaccines.⁸ Europe’s tender models and US healthcare reform put continual downward pressure on drug prices across therapeutic areas.

Technology developments are a third driver of innovation. Manufacturing technologies are evolving in response to some of these pressures. Single-use technologies have come on strongly as an alternative to permanent, reusable, stainless-steel fermentors and their attendant subsystems.⁹ An example of this trend is Xcellerex’s FlexFactory, a “plug-and-play” manufacturing platform based on the application of single-use technologies, controlled environmental modules, and process automation that includes electronic batch records.¹⁰ More technology suppliers are investing in “quick changeover” designs to aid in small batch production—for instance, full turret replacements on high-speed tablet presses.

Value-chain inefficiencies also spur change. Today, supply chain leaders struggle in a world vastly more complex than that of a decade ago. Markets with new requirements, nuanced partnerships, new global suppliers, and huge counterfeiting risks are pervasive. Those challenges add up to increased transaction costs, forcing manufacturers to re-evaluate how they manage inventory and risk across their networks.

And more of the pie is up for grabs. Now pharmas not only must be alert to credible **competition** from emerging markets—particularly from powerful, fast-growing, well-funded conglomerates in India and China—but also must be on guard to possible competitors within the pharma value chain—such as healthcare payers, partners, and distributors.

Any of these forces would drive transformation in manufacturing. Considered together, they demand a different type of response. The biggest roadblock

7 Averages for the periods 1995–2001 and 2002–2005, respectively, in: Henry G. Grabowski and Margaret Kyle, “Generic Competition and Market Exclusivity Periods in Pharmaceuticals,” *Managerial and Decision Economics*, June–August, 2007.

8 Orin Levine, “10 Years of Vaccine Progress in 10 Days,” *The Huffington Post*, June 2011.

9 Lorna D. McLeod, “Advances in Bioprocessing,” *BioProcess International*, May 2009.

10 “Novavax and Xcellerex Announce Collaboration to Develop Large-scale Manufacturing Process for 2009 H1N1 Influenza VLP Vaccine,” joint press release, Novavax and Xcellerex, October 21, 2009.

for leaders in pharma operations is less about whether to innovate and more about how to do so. How do we begin to envision the pharma plant of the future?

Three glimpses of Plantopia

What does Plantopia look like? There is no one true answer to that question. But there are other questions that will help pharma business leaders start to place more of the right kinds of bets on future production arrangements. We envision three potential archetypes for the future of manufacturing—options that take advantage of industry forces to create new opportunities (Exhibit 1). Each is modeled on successful manufacturing transformations in other industries.

The Intel model

What if the pharmaceutical plant of the future made a standard tablet core produced at very high speeds with state-of-the-art control systems, with precise and flexible coating processes capable of speeding an array of products to market? What if there were no gap between development and manufacturing, product launches were perfect—and costs started out as

exhibit 1

Factors	The Intel model	The Nucor model	The Disney model
Global forces	Execute massive standardization in response to global fragmentation	Move closer to the customer; model your business on their needs	Find ways to add value in a highly competitive, commoditized market
Latent or unmet customer needs	Drive unit costs as low as possible; bring innovations to market faster than the competition	Reduce the total cost while increasing service levels	Create features and experiences for which customers are willing to pay a premium
Technology	Become excellent at high-speed, standard operations, building quality into the process	Use the latest technology to reinvent the process, fundamentally changing the cost structure	Leverage technology to create new features and services
Competition	Use operating excellence to be faster and less expensive	Create a low-cost, high-service model that customers want to choose	Create the brand that competitors cannot replicate
Value-chain efficiencies	Manage partners to your standards; eliminate inefficient interfaces	Create a flexible factory to match highly variable customer demands	Expand your ownership of the value chain to include post-manufacturing services

SOURCE: McKinsey



best in class? This type of pharma plant might approach levels of operations excellence that are comparable to those of the semiconductor manufacturer Intel.

Because Intel competes on manufacturing efficiency, the chip maker considers its manufacturing network to be a strategic asset—easily as valuable as its advanced product designs. “Intel makes approximately 10 billion transistors per second,” said Brian Krzanich, senior vice president and general manager of Intel’s Manufacturing and Supply Chain. In response to the October 2010 announcement that Intel would be investing up to \$8 billion in future generations of manufacturing technology in the United States, Krzanich stated: “Our factories produce the most advanced computer technology in the world, and these investments will create capacity for innovation we haven’t yet imagined.”

Intel’s continual investments in manufacturing expertise enable the company to produce a new crop of chips about every 18 months that are less expensive and use less power, which is most important today as the competition shifts to tablets and smartphones.

Additionally, Intel’s emphasis on manufacturing efficiencies gives it speed and agility; the company has steadily trimmed the time needed for each step in the chip-making process. Intel also can handle product changeovers more quickly to cope with fluctuations in demand. Krzanich went on to note that Intel’s agility helped it to fix a problem and replace a flawed chip design so quickly that the disruption did not hurt revenues. This flexibility also will shorten the time it takes for Intel to ramp up new products, such as its 22-nanometer chip designs.

Intel’s argument is that functional integration—between product design and production—leads to higher average selling prices. The company reports that new process technology saves money in the long run, and is less expensive, in total, than the cost of building new fabrication facilities—each typically costing \$6 billion today, plus \$1 billion to \$2 billion for a pilot line and \$500 million to \$1 billion for an R&D process team.

Two examples of Intel’s manufacturing strategy are worthy of closer attention. Its design for manufacturability (DFM) discipline—not unique to Intel—is a way to proactively address product issues early in the design cycle. It provides a means for integrating specific manufacturing concerns into a product design in order to develop a product that is easier to manufacture with excellent overall quality. A key rationale for DFM is that not all process and layout interactions can be covered or anticipated by design rules. Since manufacturability

improvements are dynamic, new learning is included as the technology evolves.

Intel also follows its Copy Exactly! philosophy in its fab, sort, and assembly test facilities. Copy Exactly! enables the delivery of products from multiple production sites, which operate as a virtual factory that performs consistently and independent of the manufacturing source site. Additional benefits include greater consistency to quality performance and faster production ramp-ups that improve product availability.

This version of pharma Plantopia would require full integration, beyond QbD, as well as standard platforms in design and operations. The plant would be highly automated, with Six Sigma performance levels on all key quality parameters. Process controls would be well known and continuously refined. Equipment would be highly precise and ultra fast. Product quality would be built in, and truly scientific process knowledge would exist in both the development and manufacturing groups. Highly skilled technicians would propel continuous improvement in process controls and product design. All designs that did not align with the common platforms would be sourced to contract manufacturers or partners. And products would remain cost-effective long after patent expiry.

In this ideal world, products could conceivably come to market in half the time it takes today. Products would launch on time and at quality, and manufacturing processes would be capable of full-scale production within days, not months, after launch. Moreover, product cost would be best in class, independent of the product's time on the market.

Millipore offers a glimpse of what is possible. The life sciences company was able to develop unique, low-cost disposable systems—using bags instead of tanks—that are designed for fast set-up, integrated quality checks, and error-proofing. The systems and unique end-to-end process knowledge was one of the reasons why it was acquired in 2010 by MerckSerono for more than US\$7 billion. The sale represented a 50 percent market premium, partly also reflecting that securing a manufacturing innovator held some promise for a pharma manufacturer.

The Nucor model

Imagine if the pharma plant of the future were located right next to the hospital, delivering just the vials needed at exactly the right time. Then envision the plant being so small that it could be built and connected to the pharmacy—and almost be mistaken for a one-hour photo booth. Next, think what it would be like if the only operations required were replenishing the pre-qualified active pharmaceutical ingredients (API), which could be ordered automatically and with quality operations embedded in every step. That kind of

pharma plant might come close to the small-batch, premium customer service demonstrated by steelmaker Nucor.

A master of small-batch production, Nucor is known as a highly successful operator of steel mini-mills, which the company locates close to its customers. Today's mini-mills are economical at a tenth of the scale of large integrated mills. They can turn operations on and off to match production runs to market demand, and require 60 percent less energy to run compared to traditional mills.

Beginning in the late 1960s, Nucor was among the first steel companies in the United States to use electric arc furnaces to melt recycled steel—a far simpler and cheaper way to make steel than the large-scale methods then used by the big integrated steelmakers of the day. Its highly flexible production capability allows the company to almost instantaneously adjust output to match demand, and its small scale and easy access to incoming materials—with the bulk of raw material coming from scrapped vehicles—make proximity to customers easy to accomplish.

Initially, Nucor made only concrete reinforcing bars (rebars), the simplest and lowest-margin of all steel products. The company grew over time to develop further capabilities and broader ambitions. It mastered electric arc furnace technology and led the way in using recycled stock as a way to re-invent rolled steel production. Pairing this small-scale, low-cost model with high service levels, Nucor was able to disrupt the then-dominant steel-making business models and fundamentally change the game in the industry.

Nucor has continued to innovate. Collaborating with two other steel companies, the company operates a factory that continuously casts sheet steel directly from molten steel, obviating the need for heavy, expensive, energy-consuming rollers. The process, known as Castrip¹¹, has the potential to allow an entire mill to be built in one-sixth of the space needed for a mini-mill and at 10 percent of the cost of a traditional integrated mill. At the same time, Nucor is exploring lower-cost sources of iron in Australia and Brazil.

The Nucor version of pharma Plantopia would require tight integration with API suppliers and a rethinking of the entire form/fill/finish (or granulation, compression, coating for solids) process. Filling operations would be radically compressed to just the core value-adding steps. Clean-in-place systems would be fast and highly effective. Quality would be entirely automated and would take advantage of the latest high-speed chromatography technology that is embedded in the manufacturing process. Packaging would be highly standardized and inexpensive. Labeling requirements would be homogenized,

11 "The Castrip Story: Formation of Castrip LLC," *Castrip.com*, 2011.

with precision printing integral to the operations. Work-in-process inventory would not exist for more than a few minutes. “Operators” would be independent, skilled mechanics working in tandem with a sophisticated central manufacturing management system that tracks and trends operating data, helping with rapid root cause problem solving and enabling remote repairs.

Technology like this already exists in pharma in the form of blow-fill-seal, where an aseptic environment is created around the product. This technology delivers products as low as half the cost per unit and about 30 percent of the total floor space of a conventional aseptic filling line. There are further savings in cost and space because the need for dedicated HVAC equipment is minimized, and the lines can occupy 50 percent less space. Yet, this technology, which was developed eight decades ago, is only in limited use, primarily by contract manufacturers and for non-core products.

The Disney model

What if the pharma plant of the future not only consistently delivered high-quality products at low cost but also tracked and trended patient behavior, using real data to improve efficacy and patient compliance—potentially saving health-care systems billions of dollars in waste? What if there were a smartphone app for your pill that let you know all of the drug’s interactions? What if that pill came with complete manufacturing traceability and round-the-clock service support? What if patients could pull up their own full pharmaceutical history in the doctor’s office by scanning their pillboxes? That model for pharmaceutical operations might approach the Disney model in terms of value-added services and experiences beyond the core product delivery.

If Intel and Nucor shine the spotlight on fresh perspectives for pharma manufacturing, Disney draws attention to complementary operations areas that are ripe for innovation. Where once Disney could have been described as a media company—largely built around film—today it is an entertainment conglomerate with interests that range from theme parks to hotels to gaming to product franchises.

Disney successfully leverages its brand not only for its own benefit but also for the benefit of a raft of value-chain partners whose success continues to amplify Disney’s core brand. Just one recent example: Toy-maker Mattel has seen sales soar on the strength of merchandise sales tied to the *Cars 2*

animated movie, a product of Disney's Pixar studios.¹² Since Disney is eager to offset the soaring production costs of big movies and the steep drop in DVD sales, the company is keen to spread its risks by focusing on films that can more easily generate sequels and spin-offs, as well as games, theme-park attractions, and a host of toys and other themed merchandise.¹³

The Disney Plantopia model would require pharma business leaders to view their organizations in different terms—to manage data and systems in the same way that they do pills and vials. It would call for a rethinking of the usual boundaries of operations so that pharma business leaders could readily draw data and insights from customers' use of their products. The packaging would have scannable information for consumers to access on their smartphones. The vial or pill would have an embedded microchip to relay information about patient behavior, intake time, and the drug's effects. The clinical trial data would be evergreen, continually refreshed with new and insightful patient data. The regulatory approval process would rely on incredibly robust data. And the operating group would include a call center staff as well as an information management and programming group.

Some technology for this type of approach already exists to address counterfeit drug traffic in Africa. A consumer can scratch off the label on a pharmaceutical product and text Sproxil, a small company that can verify if the product is real or fake and inform the consumer via a return text message.¹⁴

There are other parallels in the experiences of Medco Health Solutions, the pharmacy benefits provider spun off by Merck in 2003. Medco is innovating by using the health-related information it has been gathering for years from its fast-growing subscriber base—a by-product of its investments in highly automated pharmacy operations. This innovation has led to a multibillion-dollar incremental business.¹⁵

The company has expanded by opening nine therapeutic resource centers in the United States that are staffed by more than 1,100 pharmacists trained in one of a dozen or more chronic diseases. These specialists use the information available through Medco's vast database to help patients manage their health problems. Target customers are people who suffer from chronic and complex conditions such as diabetes and cardiovascular problems; they account for 90 percent of all drug spending and 75 percent of all healthcare costs. The database enables the pharmacist to tell if a patient is taking the medication as prescribed, or if a particular test is needed. Such interventions

12 Maxwell Murphy, "Cars 2' Drives Up Mattel's Profit," *Wall Street Journal*, July 15, 2011.

13 Ethan Smith, "Disney's 'Cars 2' a Hit Already—in Stores," *Wall Street Journal*, June 20, 2011.

14 Clark Boyd, "Cell Phones Help Fight Fake Drugs in Nigeria," *discovery.com*, April 15, 2010.

15 "The Case for Infrastructure Investment: Lessons from Medco and Staples," *SCRM* editorial, *Supply Chain Management Review*, September–October 2011.

not only can improve patient outcomes but also can mean cost savings for Medco's clients—the employers, health plans, and government agencies that hire Medco to keep their members healthy while controlling prescription and medical costs.

Sanofi-Aventis has taken a similar lead in the diabetic therapeutic area. In 2009, the company launched an iPhone app to help diabetics count calories. And in 2010, they launched the iBGStar hybrid medical device—a standalone glucose monitor that has the added functionality of connecting to an iPhone or iPod touch to allow users to manage their own data.

From here to Plantopia

Rather than limit pharma leaders to three choices, the Intel, Nucor, and Disney models are intended to foster fresh thinking about how each individual pharma company can leverage manufacturing operations to quickly and reliably boost value for its shareholders.

The most important question is how and where to get started. There may be different business models for different markets. Would rural China have the same profile as urban Western Europe? Would small-molecule generics and novel biologics share the same model?

Each company's leadership team must determine who "owns" the discipline of innovation in operations. Is manufacturing able to reinvent itself, or should a collaborative, cross-functional team take on the challenge? What type of leader is needed to drive the organization toward innovation?

Once the company's leaders have defined the innovation owner and selected which customer groups to target, they must determine which innovations matter most for these market segments. What are the challenges that will best inform the innovators? How have others solved similar challenges? What can be achieved through licensing or partnerships? What are business leaders outside of pharma doing?

Pharma CEOs have a duty to hold their top teams to task in light of the need for innovations in production. The CEO needs to raise the bar on what is expected from the manufacturing group and challenge the operations group to detail a clear picture of what the future state can look like. Leaders must bring in new ideas, challenge conventional thinking, and invest in a portfolio of ideas. CEOs must look at manufacturing as more than a cost center and demand that operations go beyond incremental improvements alone.

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Other industries have pushed manufacturing innovation far and fast. Of course, that by itself is not a reason for pharma leaders to follow suit, but the seismic shifts in the industry's economics certainly are reason enough.

There is a clear, competitive rationale to act now. Innovation within pharma manufacturing is still an open field with no clear leader. There is still a huge opportunity to use manufacturing operations as a strategic growth tool. There are a host of potential partners and an abundance of opportunities for far-sighted manufacturing leaders to emerge and be recognized as industry change makers. Who will be the first to realize the Plantopian ideals?