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Continuous manufacturing in pharmaceuticals: Economic and policy issues



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I. INTRODUCTION

In the pharmaceutical industry, the development of new products is followed by the entry of generic products after patent expiration. This product life cycle and the benefits it provides to consumers in the healthcare sector has received a great deal of attention from economists, who have studied the value of innovative therapies and the vigorous price competition resulting from generic entry. The economics of prescription drug manufacturing, however, has received far less attention. The maintenance of a competitive market for generic medications depends on companies' continued ability to manufacture medicines at low cost.

This report takes a high-level economic view of current issues in manufacturing of pharmaceuticals and changes in manufacturing technology. Changes in manufacturing technology are not unique to the pharmaceutical industry. Advances in technology have led to substantial changes in a variety of manufacturing industries over the past century or more, including steel, petroleum products, construction materials, and many more. New discoveries have led to advances in manufacturing technology, new ways of organizing production, and changing costs.

Important issues arise as governments seek to encourage the adoption of new manufacturing technologies, particularly in highly regulated industries. Progress brings with it the potential for greater efficiency and novel ideas. However, the pharmaceutical industry and the regulatory environment in which it operates are significantly more complex than the average manufacturing sector. Of particular note is the concern about shortages of generic prescription medicines and price increases for established products that seem to belie the presumptively competitive nature of the market for such products.¹ The economic and strategic forces driving technological change in the pharmaceutical sector warrant additional consideration.

The impact of potential changes to pharmaceutical manufacturing technology, and its regulation in particular, is intertwined with other trends in the pharmaceutical supply chain that have attracted the attention of policy makers and academics. Recent trends include greater consolidation in the health insurance, pharmacy benefit manager (PBM), and pharmacy sectors; increased introduction of specialty products; and the emergence of biosimilars. Changes to the pharmaceutical manufacturing sector should be viewed in the context of the also-dynamic drug supply chain.

The FDA has expressed the view that continuous manufacturing (CM) has a role to play in solving several problems, including shortages and prescription drug quality concerns.² However, changes to manufacturing technology and subsequent regulatory changes affect the conditions of entry and exit into generic drug markets. In particular, there is a risk that these changes could exacerbate rather than alleviate concerns about availability and prices of prescription drugs. This could happen for a variety of reasons. For example, the development and implementation of CM may only be economical for large-scale, high-margin manufacturing. If products manufactured through CM become more costly for generic entrants to replicate and manufacture, it is possible that generic competition would be diminished, with the number of potential suppliers shrinking. A diminished

1 Selected publications on drug shortages and related issues include: Christopher Stomberg, "Drug Shortages, Pricing, and Regulatory Activity" (NBER Working Paper No. 22912, Dec. 2016); Ali Yurukoglu, Eli Liebman, and David B. Ridley, "The Role of Government Reimbursement in Drug Shortages" *American Economic Journal: Economic Policy* 9, no. 2 (2017): 348–82; Murray L. Aitken, Ernst R. Berndt, Barry Bosworth, Iain M. Cockburn, Richard Frank, Michael Kleinrock, and Bradley T. Shapiro, "The Regulation of Prescription Drug Competition and Market Responses: Patterns in Prices and Sales Following Loss of Exclusivity" (NBER Working Paper 19487, Oct. 2013); and Rena M. Conti and Ernst R. Berndt, "Specialty Drug Prices and Utilization after Loss of U.S. Patent Exclusivity, 2001–2007" (NBER Working Paper No. 20016, Aug. 2014); US Government Accountability Office, "Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge" (GAO-16-595, June 2016), available at <http://www.gao.gov/assets/680/678281.pdf>; US Government Accountability Office, "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability" (GAO-14-194, Feb. 2014), available at <http://www.gao.gov/assets/670/660785.pdf>.

2 See, e.g., Michael Kopcha, "Continuous Manufacturing—Common Guiding Principles Can Help Ensure Progress," *FDA Voice*, Sept. 11, 2017, available at <https://blogs.fda.gov/fdavoices/index.php/2017/09/continuous-manufacturing-common-guiding-principles-can-help-ensure-progress/>.

generic manufacturing base is less capable of acting as a market-based solution for product shortages and increasing prices. These are important issues that policy makers and industry thought leaders ought to consider.

This paper reviews the basics of pharmaceutical manufacturing and discusses CM in the context of the economics of the prescription drug industry. It discusses the likelihood that greater adoption of CM will lead to positive outcomes for domestic manufacturing and considers the macro-level costs of transitioning from batch to continuous processes. It concludes with a brief discussion of public policy considerations.

II. MANUFACTURING IN THE PHARMACEUTICAL INDUSTRY

The manufacturing of pharmaceutical products is highly varied. Medicines come in a wide range of dosage forms and administration routes and vary in their complexity. Particularly in the United States and other developed countries, pharmaceutical manufacturing is subject to extensive regulatory oversight to monitor safety and consistency of manufacturing processes. In large measure, this regulatory structure has resulted in pharmaceutical manufacturers making relatively few changes to manufacturing processes over time. Because any change in manufacturing processes leads to a time-consuming and costly regulatory review process, it is typically in a manufacturer's economic interest to make far fewer changes to an approved manufacturing process than it otherwise might.³

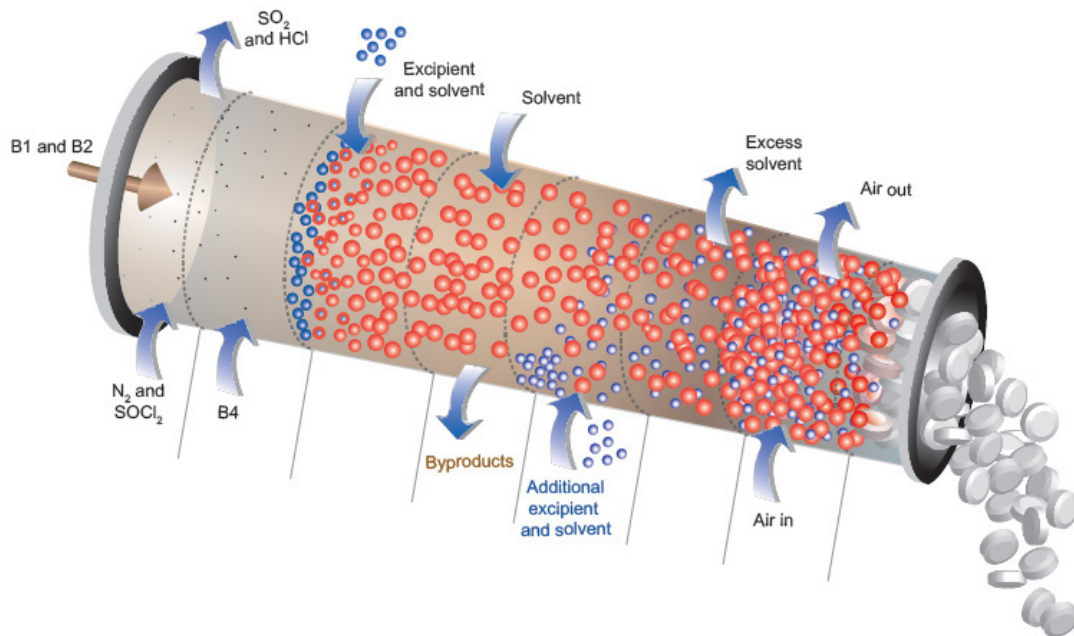
Over the past few decades, manufacturing processes across different industries have moved, to a small or large extent, from what is typically referred to as "batch" processes toward "continuous" processes. Although the dichotomy is imperfect because true continuous, or "end to end" manufacturing without batch elements is rare, it is useful for the purposes of this discussion to characterize existing pharmaceutical manufacturing technologies as either batch processes or continuous processes.

II.A. Batch vs. continuous manufacturing

Traditionally, pharmaceutical manufacturing has been done in batch mode. Although batch processes generally have some in-process monitoring, they typically involve sequentially loading quantities of materials, processing the mass, and then discharging the transformed material. At the end of a batch process, the output is evaluated and a determination is made about whether the "batch" satisfies specifications and can either be moved on to a next stage of production or processed for shipping to the marketplace. Continuous pharmaceutical manufacturing, in contrast, involves material being constantly loaded, processed, and unloaded without interruption. Semi-continuous operations have elements of both batch and continuous, in which materials are either constantly loaded or constantly removed from the process, but not without interruption.

In contrast to batch manufacturing, CM is thought of as a process that flows from beginning to end without major interruptions or breaks in the process. A stylized but common representation of such a process is illustrated in Figure 1 below.

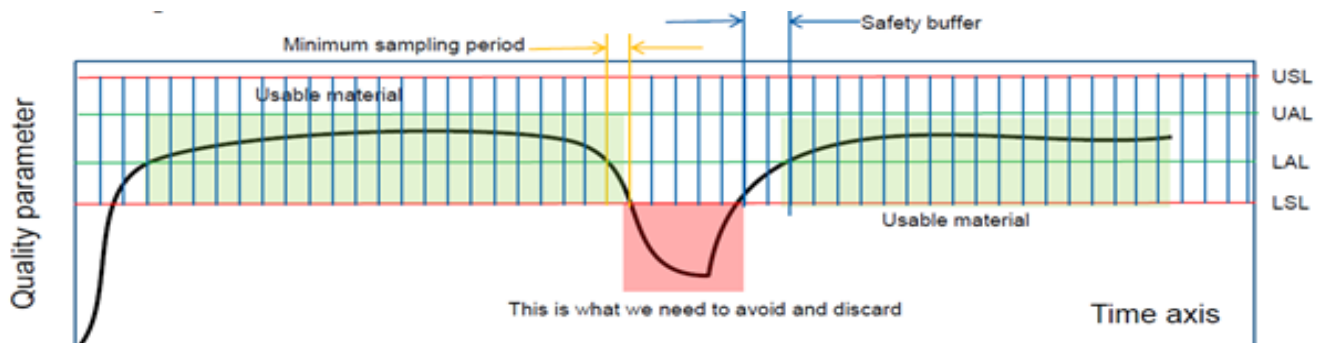
³ The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is working to address this challenge through creation of its Q12 guidance, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. The eventual impact of this guidance is unknown at this time.

Figure 1 – Stylized illustration of end-to-end manufacturing

Source: 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals; Implementation, Technology & Regulatory; Massachusetts Institute of Technology; Sept. 26–27, 2016, available at <https://iscmp2016.mit.edu/>.

One of the advantages of CM is that such processes typically allow continuous in-process monitoring of product quality and chemical or biological reaction so that problems can be identified, isolated, and addressed before a complete batch of output is completed. As illustrated in Figure 2, the real-time identification of a process that has gone outside of specifications allows for intervention and resolution without “spoiling” the entire batch, as might be the case if such in-process monitoring were not available.

Additional technical advantages CM that are discussed in the literature include smaller physical footprint, lower labor requirements (although higher skilled labor is needed), greater flexibility in starting and stopping processes, and greater quality control and consistency.

Figure 2 – Illustration of gains from monitoring in CM

Source: Presentation of Markus Krumme, CM Unit Head, Novartis, Sept 26, 2016. Available at: https://iscmp2016.mit.edu/sites/default/files/documents/Novartis%20E2E%20case%20study%20Final_NEW.pdf. Accessed June 29, 2017.

Pharmaceutical manufacturing varies substantially across product types. The technical advantages of CM may be more or less important, depending on the circumstances, and in some cases may not correspond to economic advantages. Certain experts have expressed the view that the benefits of CM are likely to be found in large-scale manufacturing, and particularly in high-margin products.⁴

III. THE STRUCTURE OF THE PHARMACEUTICAL INDUSTRY

To appreciate the economic issues surrounding technological change in pharmaceutical manufacturing, it is helpful to understand the role of manufacturing in the industry and the differences that role plays in different sectors within the industry. We begin with a brief overview of the pharmaceutical industry and the forces that drive it.

In general, modern prescription drugs are formulated as a result of research and development (R&D) investments. These investments tend to be large, occur over a long period of time, and have highly uncertain payoff. Relatively few products that begin the development phase make it to market, and many that ultimately receive approval generate modest amounts of revenue. The business model is one in which “blockbusters” have traditionally provided the revenue necessary to keep the R&D enterprise going.⁵

New drugs are protected by patents or other forms of regulatory exclusivity for varying amounts of time, depending on the product. During the period of market exclusivity, brand-owning manufacturers typically spend substantial amounts of money on marketing and promotions to introduce their products to patients and prescribing physicians. Products that provide a solution to a patient’s needs will be widely prescribed and, while protected from competition, will sell at a substantial margin above cost.

During the limited period of exclusivity, a brand manufacturer is typically more focused on sales than on manufacturing costs. This is not to suggest that they are not interested in cost saving, but rather that they are more focused on assuring that demand is met during the finite time the product is protected by exclusivity. Given significant margins typically earned by a branded drug, the risk of not having sufficient stocks of product to fill demand is a substantial potential cost. Hence, while brand manufacturers do indeed gain experience with manufacturing processes over time, the risk of interfering with a manufacturing process that reliably provides product at an acceptable cost is greater than the relative return on seeking low-cost manufacturing. Making substantial changes to manufacturing processes not only runs the risk of interfering with production and stock out, but also runs the risk of regulatory delay in obtaining approval for new manufacturing processes. It is notable, for example, that the Food and Drug Administration’s (FDA) first approval of a switch from batch to CM took five years to accomplish.⁶

Once exclusivity is lost, other potential suppliers—typically generics manufacturers—are able to gain approval of an abbreviated new drug application (ANDA). Successful ANDA applicants can sell generic copies of drug products. While meaningful investment is still required, the risk and cost of obtaining such approval is lower than

4 Interview with Richard D. Braatz, PhD, Edwin R. Gilliland Professor, Faculty Research Officer, Department of Chemical Engineering, Massachusetts Institute of Technology, conducted March 2017.

5 The economics of the industry are well described in several chapters of Patricia Danzon and Sean Nicolson’s *The Oxford Handbook of the Economics of the Pharmaceutical Industry*. (New York: Oxford University Press, 2012). In particular, the blockbuster model is described by Joseph DiMasi and Henry Grabowski in chapter 2 of that volume: “R&D Costs and Returns to New Drug Development: A Review of the Evidence.”

6 See Eric Palmer, “FDA Urges Companies to Get on Board with Continuous Manufacturing,” *FiercePharma*, Apr. 14, 2016, available at <https://www.fiercepharma.com/manufacturing/fda-urges-companies-to-get-on-board-continuous-manufacturing>.

the cost of a new drug application (NDA), and many companies have traditionally sought approval to sell each generic medicine once branded exclusivity has expired. Generic drugs tend to be sold in competitive markets driven by price competition that, when/if it operates as envisioned under the Hatch-Waxman Act, fits the economic model of a competitive industry very closely.

In particular, among generics manufacturers, because competition tends to drive prices down over time, and because generics of any particular drug from different manufacturers are interchangeable, generic manufacturers' attention is focused more on manufacturing cost efficiencies. Lowering manufacturing and overhead costs is essentially the only tool available to a generic manufacturer to improve operating profits and continue to compete on prices. Hence, it is not too much of an oversimplification to suggest that generics focus on cost efficiencies to a more serious degree than do their brand counterparts, which helps explain why brand manufacturers generally yield market share to generics following loss of exclusivity rather than try to compete with them on price.

In economic terms, a competitive market is one in which barriers to entry and exit are low. This means that if the price of a product rises above the cost of supplying it and companies in the industry are making above-normal profit levels, new companies will be enticed by the profit opportunity to enter the industry and begin selling the product. This entry, however, will increase supply and tend to drive the product's price down to the level at which profits are restored to normal levels. At that point, when companies are no longer making above-normal profits—and indeed some may be making less than normal profits—companies are induced to exit such that in equilibrium, prices remain at levels that neither entice new entry nor induce exit. To reiterate, in the ideal setting, the generic drug industry would follow the model of a competitive market quite closely. Prices should not typically stray far from the cost of supply unless some barrier arises that raises the cost of entry or exit. Potential barriers include regulatory restrictions that may artificially delay entry or exit. In this context, the regulation of manufacturing processes is important to get right, since if inefficient restrictions are put in place, or if incentives to undertake inefficient manufacturing practices evolve, the competitiveness of the generic drug industry can be interrupted which can potentially lead to supply shortages and higher product prices.⁷

Another important distinction between the branded and generics sectors is that marketing is rare for products that have lost market exclusivity. By the time a product loses exclusivity, the relevant physicians are typically familiar with the product, so marketing and promotion has less productive potential. Moreover, since generic drugs are by regulatory definition interchangeable at the pharmacy, marketing by any one supplier would have significant spillover effects on sales of competitors, so the incentive to market generic products is limited.

These factors help explain why the markets for branded and generic drugs work the way they do and some of the concerns and controversies about drug manufacturing, drug shortages, and innovation in the manufacturing process. The implications for changing manufacturing technology are likely to be quite different in the brand and generics sectors, and a recognition of these differences should guide thinking about the policy environment involving pharmaceutical manufacturing.

A key distinction between the competitive economic model and the practical reality of the generics industry has to do with manufacturing regulation, consolidation of purchasers, and other barriers to entry, which have received far less attention than the price side of the generics sector. These are important issues, however, as reflected in the evidence that entry and exit conditions in the generics sector are changing, potentially harming the competitive environment.

⁷ Indeed, recent economic research points to the emergence of less competitive conditions in the US generics industry tied to recent changes in regulatory policy such as the passage of the Affordable Care Act and the implementation of Generic Drug User Fees. These conditions include a reducing tendency for entry and increasing tendencies for exit in generics markets which results in fewer suppliers per product and somewhat higher product prices over time. See Ernst Berndt, Rena Conti, and Stephen Murphy, "The Landscape of US Generic Prescription Drug Markets, 2004-2016" (NBER Working Paper 23640, July 2017) and "The Generic Drug User Fee Amendments: An Economic Perspective" (NBER Working Paper 23642, Aug. 2017).

III.A. Growth of the generic drug industry

The generics industry has grown rapidly since the passage of the “enabling” Hatch-Waxman Act of 1984. Growth has been fueled by the expiration of patents on many highly used drugs in recent years. Presently nearly 90% of US drug prescriptions are filled with a generic, and sales of generics have risen by more than 500% over the past two decades. According to the Association for Accessible Medications, ten top-selling generic products generated savings of nearly \$76 billion to patients and the health care system in the United States in 2016.⁸

Coincident with the growth of the industry has been a wave of consolidation and change. The list of top generics companies from 20 years ago bears little resemblance to the same list today. This is driven in part by the establishment of a biosimilars pathway, which has drawn both traditional generics companies and traditional brands into this new market, blurring the distinction between the two sectors. These dynamics are also heavily influenced by regulatory, market, and legislative changes that have incentivized larger scale in the generics industry. Moreover, in recent years, rapid price increases for certain products and shortages of key generic drugs have given rise to concern about the competitiveness of the industry.⁹

In response to some of these concerns, the FDA has reportedly sought to encourage the modernization of pharmaceutical manufacturing.¹⁰ While such efforts have impact on both innovator and generic manufacturers, the differing business models between the sectors suggest that the implications of manufacturing approaches, and the regulatory framework in which manufacturing takes place as it relates to generic drugs, merits exploration.

III.B. The stability of company-specific demand has important implications for CM

The adoption of new manufacturing technology involves the investment of money and other resources. Not only must plant and equipment be acquired, but regulatory approval must also be managed. As with any economic decision, uncertainty about the return on an investment (all else the same) reduces the likelihood that the investment can be made, so the companies that are more likely to be able to adopt novel CM processes are those that have a relatively high degree of visibility into the return on their investments. During the time they are protected by patents and other forms of exclusivity, companies making branded medicines are likely to face a far more stable and predictable demand, with much higher profit margins, than are the manufacturers of generic drugs.

Hence, in evaluating the likely adoption of CM technologies and techniques, it is important to understand the degree to which company-specific demand differs between brand and generic products. When innovative products lose exclusivity and generic entry begins, it is common for the first entrant (or joint entrants in some cases) to gain a brief period of market exclusivity during which they are protected from entry by other sellers. However, following these periods, it is common for entry to follow and for the advantage the first mover(s) experienced to dissipate. It is also common for entry and exit of competitors to continue over time.

⁸ Association for Accessible Medicines, “Generic Drug Access & Savings in the U.S. 2017,” p. 19, available at <https://accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf>.

⁹ See Berndt et al., *supra*, note 7.

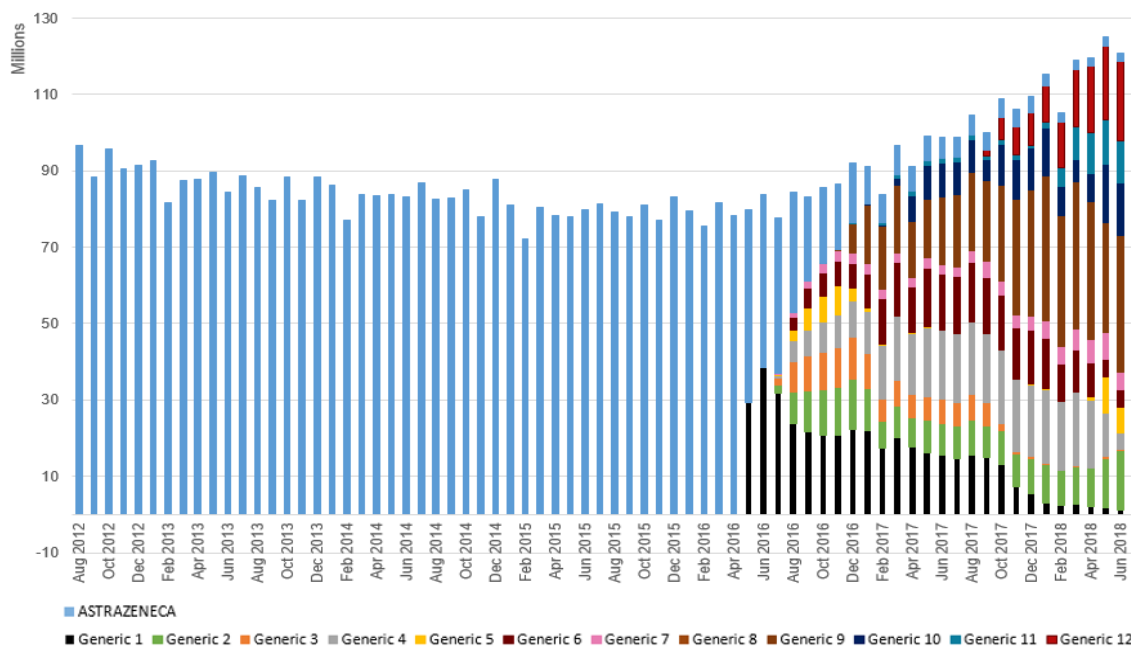
¹⁰ See, e.g., Sharmista Chatterjee, “FDA Perspective on Continuous Manufacturing,” Presentation, IFPAC Annual Meeting Baltimore, Jan. 2012, available at <http://gmpua.com/Process/ContinuousManufacturing/ContinuousManufacturing.pdf>; Joanne Eglovitch, “Pharma Industry Still Not at ‘Tipping Point’ in Adopting Continuous Manufacturing,” *Pink Sheet*, Apr. 25, 2017, for a discussion of the commentary at the 3rd FDA/Product Quality Research Institute conference on Advancing Product Quality, March 22–24, Rockville, MD; and Meg LaTorre-Snyder, “The Benefits of Continuous Manufacturing,” *R&D Magazine*, Dec. 28, 2016, available at <https://www.rdmag.com/article/2016/12/benefits-continuous-manufacturing>.

The result is that any particular company in the generic sector has relatively unstable and unpredictable demand for its product, particularly as compared to the originator product it follows onto the market. These competitive forces also tend to result in falling prices and reduced profit margins. The instability of future demand and the uncertain profit margins to be earned suggest that it would in many cases simply be uneconomical for even the larger generic manufacturers to make significant investments of time and resources necessary to adopt CM technologies.

The figures below illustrate the difference in stability of demand between the brand and generic sectors. First, to illustrate the pattern of competition, Figure 3 and Figure 4 show the pattern of monthly sales of two notable products that have lost exclusivity in the past five years: Crestor® (Rosuvastatin) and Celebrex® (Celecoxib).¹¹ The data available for these figures begin in August 2012, well after each product had been launched. By that time these products were mature and well known by prescribing physicians and many patients. In the years leading up to loss of exclusivity (LOE), each product exhibited relatively high, stable monthly sales.

The first generic sales of Rosuvastatin are recorded in April 2016.¹² The first generic entrant had exclusivity for part of the first three months, following which several different suppliers joined the market. It is notable that total utilization of the drug grows substantially after generic entry, but no generic entrant gains and maintains a large share of those sales over time. Notably, the first entrant, which sold nearly half (45.8%) of all Rosuvastatin units in the third month after it entered the market, quickly surrendered share to other entrants. One year after entry, its sales accounted for just under 20% of total units, and by the end of its second year, it accounted for only 2% of the total. Companies entering later had taken far larger shares. Contrasting the level of sales and their relative instability over time to those achieved by the originator product, it is clear that the originator would have a far greater ability to make investments into new manufacturing technologies than would any of the generic entrants.

Figure 3 – Rosuvastatin monthly sales of extended units (pills)



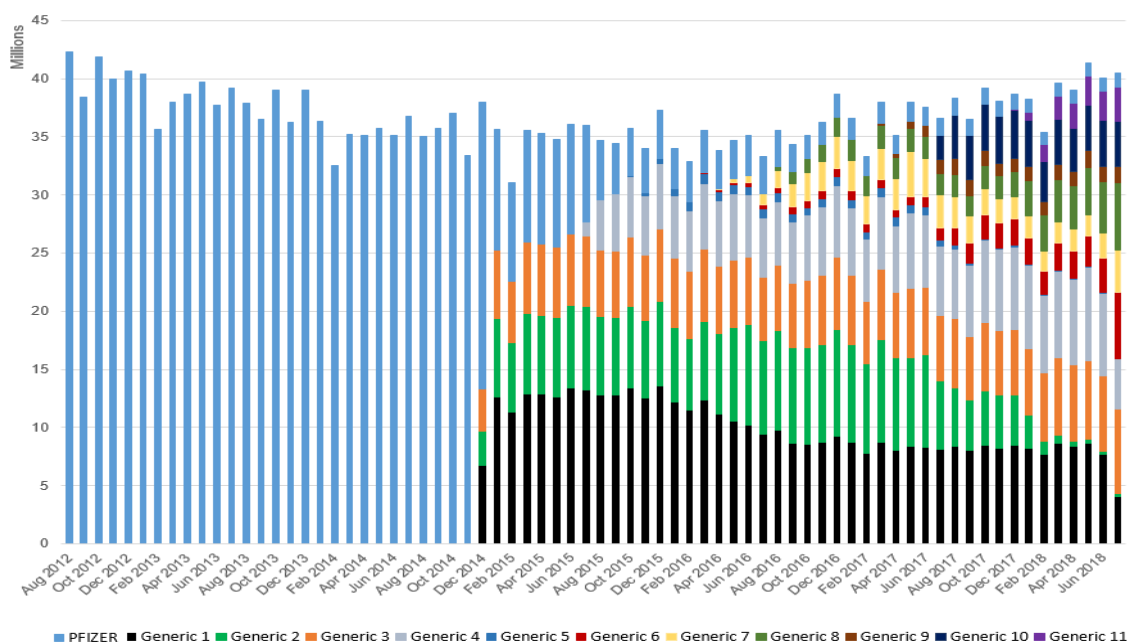
Source: IQVIA.

¹¹ The data for the charts in this section are provided by IQVIA.

¹² Sales in April are small and do not show up on the chart.

A broadly similar pattern is exhibited by the sales of celecoxib in Figure 4. Although total sales do not grow post-LOE to the extent that they did in the Rosuvastatin case, and the originator's sales were declining somewhat in the two years prior to generic entry, sales for the originator were substantially higher over an extended time, and more stable, than were the sales of the generics that followed. The data indicate that three companies entered the market with generic versions of Celecoxib in December 2014. After six months, a fourth entrant began selling and several others entered over the following two years. In this case, one of the original entrants had essentially fallen out of the market by the end of the observation period (July 2018), another had fallen to about one-third of its peak sales, and the third had maintained sales at a fairly stable, though much smaller level (around 6 million units per month) than the originator had experienced (largely between 35 and 40 million units) prior to generic entry. Once again, the ability of the originator to invest in new manufacturing technologies would have been far greater than would that of any of the following generic suppliers.

Figure 4 – Celecoxib monthly sales of extended units (pills)

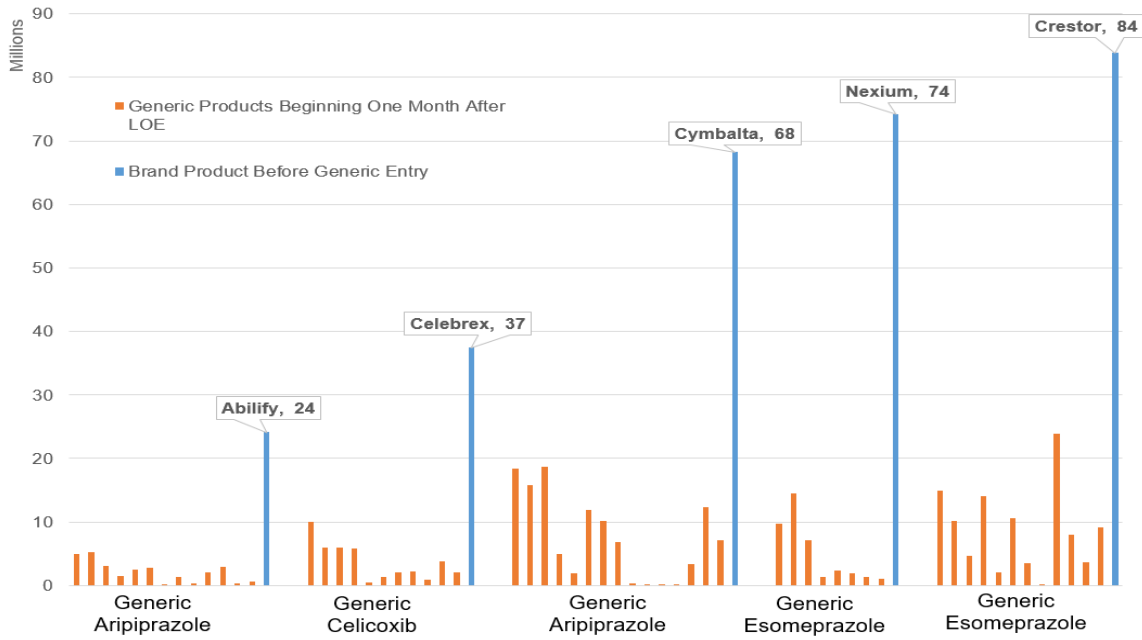


Source: IQVIA.

The patterns shown in these two examples are reasonably representative of a general pattern. For five successful prescription drugs sold in oral dosages, Figure 5 and Figure 6 summarize the differences in monthly average levels of demand and the variability of that demand between the originator and the generic companies that enter after LOE. Similar patterns exist among injectable drugs as well, as illustrated in Figure 7 and Figure 8.

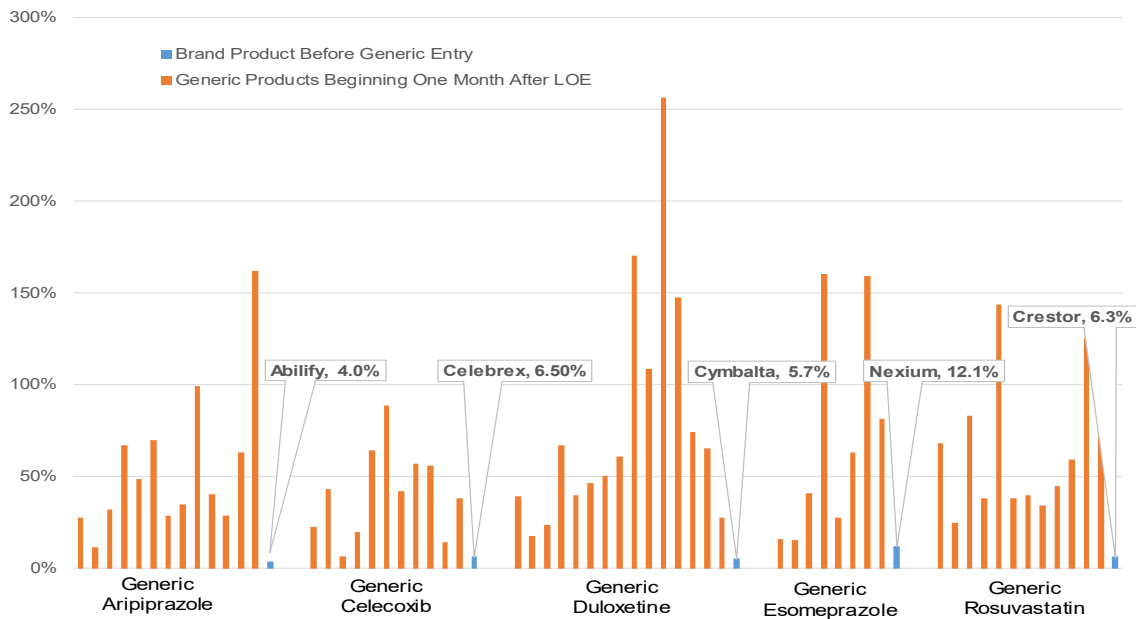
Among the oral dosage forms, the average monthly units sold by the originator in the two to three years prior to generic entry are always at least twice as large, and typically much more, as the average of even the largest generic competitor. And as shown in Figure 6, month-to-month variation in quantity demanded is far greater as a percentage of average sales for the generic manufacturers than for the originator previous to LOE.

Figure 5 – Average monthly sales, brand (pre-LOE) v. generic (post LOE)



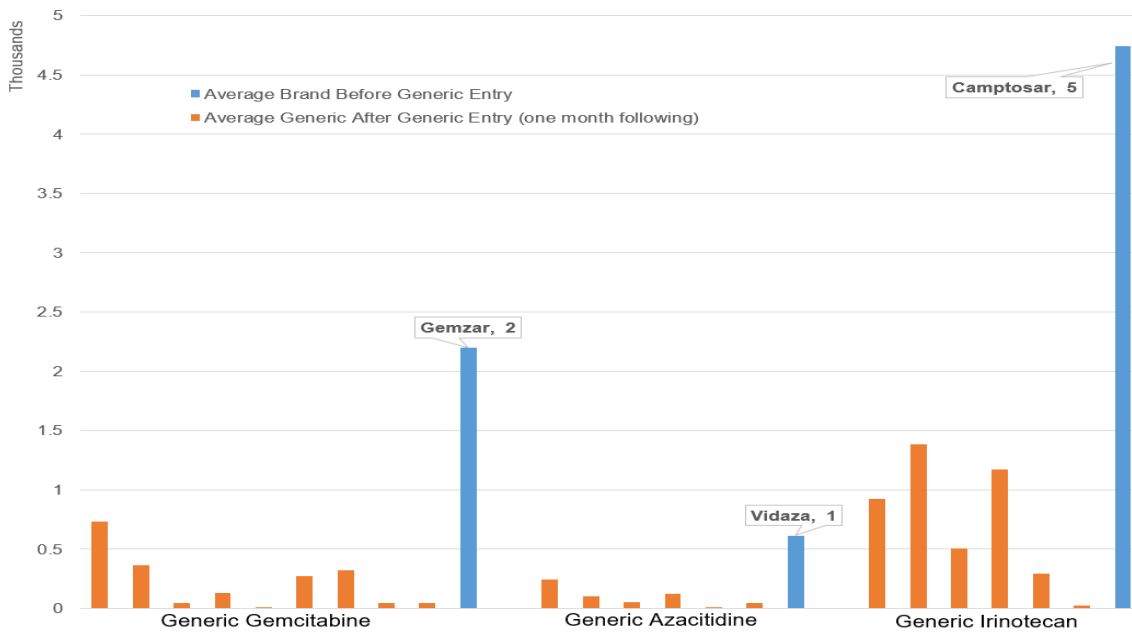
Source: IQVIA.

Figure 6 – Coefficient of variation, brand (pre LOE) v. generic (post LOE)



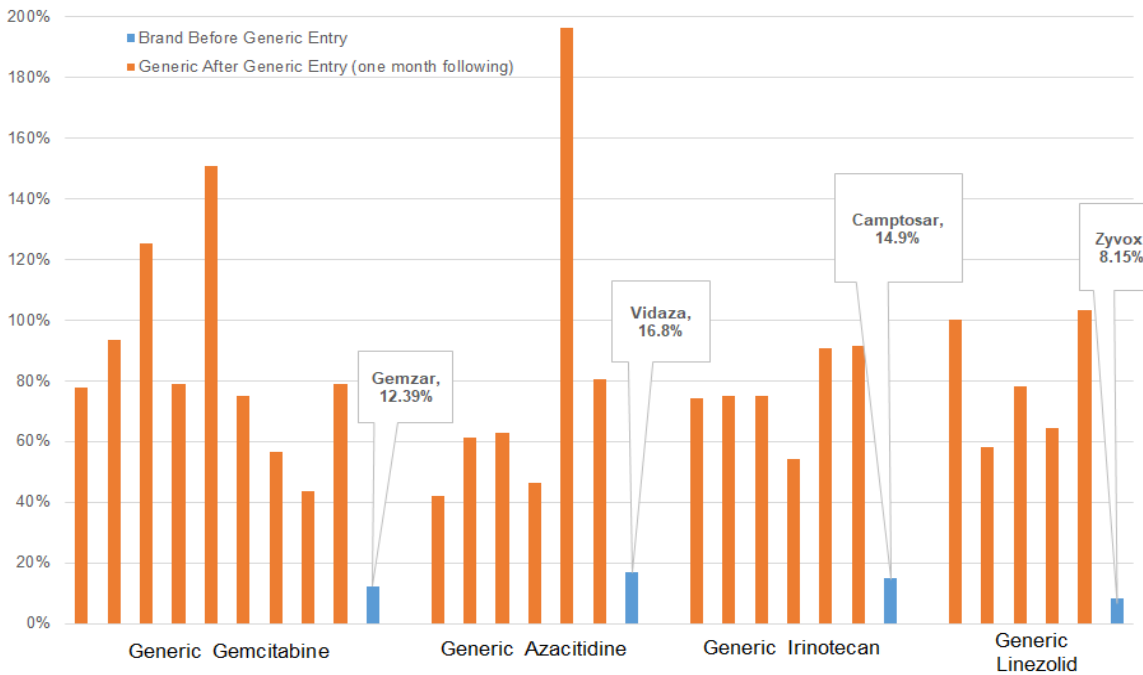
Source: IQVIA.

Figure 7 – Average monthly sales, brand v. generic chemotherapy agents



Source: IQVIA.

Figure 8 – Coefficient of variation for injectable drugs, brand (pre LOE) v. generic (post LOE)



Source: IQVIA.

In summary, the clear indication of the data reviewed here is that the typical generic entrant—indeed, most likely every generic entrant—faces lower quantity and higher variability in demand over time than did the originator product it replaces. These differences have important implications about the ability of generic entrants to make the necessary investments in CM technologies. Policy makers and regulators should be very careful not to ignore

these issues as they consider steps that would disadvantage companies that do not adopt such manufacturing processes.

IV. FDA HAS ENCOURAGED ADOPTION OF CM

In recent years, the FDA has spurred many initiatives to foster the broader adoption of CM in the pharmaceutical industry. Among other things, the FDA has participated in a series of meetings bringing industry leaders and academic experts on the engineering of manufacturing technology to discuss the barriers and opportunities available from advances in manufacturing technology; enlisted government, non-profit, and academic stakeholders; sought public input on white papers; and provided money to the private sector.¹³

The FDA believes that the greater adoption of CM could lead to lower-cost manufacturing, higher quality of output, lowering manufacturing cost, increased reliability of supply, and lower prices. Moreover, the FDA has argued that the broad adoption of CM could bring pharmaceutical manufacturing back to the United States. Part of the motivation for this may be the large burden that the inspection of foreign manufacturing facilities places on the FDA.

While there is general agreement that in many circumstances, CM processes lead to lower incremental manufacturing cost, it is less clear—after considering start-up costs, including the acquisition of new facilities and the potential abandonment of existing manufacturing capital—that CM leads to lower total manufacturing cost.

The study by Schaber et al.¹⁴ is the most commonly referenced article suggesting a large cost-reducing potential of CM in pharmaceutical manufacturing. Schaber estimated that capital expenditures would be between 20% and 76% lower in a CM facility and that overall costs would be 9%–40% lower in a CM facility manufacturing a single blockbuster drug using dedicated equipment. While this study has received a good deal of attention, it has important limitations.

Importantly, the Schaber analysis does not rely on empirical observations but is mostly the result of educated conjecture. Its analysis is based on a single scenario (a single blockbuster product), which is inapplicable to the vast majority of industry cases where multi-purpose equipment is likely needed. Moreover, it assumed, generally without evidence, that CM in-process inventory requirements would be only 10% as high as batch and that plant direct labor costs would be half those of batch. Other important assumptions in the analysis include the following:

- CM process engineering costs would be 10% higher than batch;
- A one-year construction time, and no pre-construction engineering and other planning, regulatory approval, financing uncertainties;

¹³ As an example of FDA engagement with industry and academic experts on CM, see Brookings Institution, “Promoting Continuous Manufacturing in the Pharmaceutical Sector,” Oct, 19, 2015 (meeting agenda and materials available at <https://www.brookings.edu/events/promoting-continuous-manufacturing-in-the-pharmaceutical-sector/>). In addition to this type of promotional activity, the FDA has established an emerging technology team; fostered White House focus on CM, and engaged US Health and Human Services/the Biomedical Advanced Research and Development Authority, US Pharmacopeia, and the US Department of Commerce in initiatives related to the adoption of CM. The FDA has also given a \$4.4 million grant to Continuous Pharma to set up a pilot facility for FDA’s use and purchased additional CM equipment for its own labs. See, e.g., <http://www.pharmtech.com/continuous-pharmaceuticals-partners-fda-and-barda>; <https://www.fda.gov/Drugs/NewsEvents/ucm557448.htm>; <https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Blog/NSTC%20SAM%20technology%20areas%20snapshot.pdf>; <https://obamawhitehouse.archives.gov/the-press-office/2016/04/01/fact-sheet-obama-administration-announces-new-revolutionary-fibers-and>; <http://qualitymatters.usp.org/exploring-continuous-manufacturing-technology-and-applications-pharmaceutical-industry>; <http://www.niimbl.us/>; <https://blogs.fda.gov/fdavoic/index.php/2017/09/continuous-manufacturing-common-guiding-principles-can-help-ensure-progress/>.

¹⁴ Spencer Schaber, Dimitrios Gerogiogis, Rohit Ramachandran, James Evans, Paul Barton, and Bernhardt Trout, “Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study,” *Industrial & Engineering Chemistry Research* 50, no. 17 (2011): 10083–92.

- A 15-year useful plant and equipment life (for both batch and CM), which is shorter than the average total lifespan of existing batch depreciable assets;
- A US manufacturing location and input pricing;
- Labor cost savings estimating that batch requires twice as many operators as CM and that each operator's cost would be \$160,000 per year.¹⁵

Schaber did not attempt to quantify abandonment or transition costs, e.g., capital expenditures or company and regulatory organizational change costs. Despite its lack of empirically founded analysis, this study has been widely referenced by CM advocates as an indication of the potential cost savings available from CM. It seems appropriate to view these results with healthy skepticism.

To date, CM remains in the early stages of adoption by industry.¹⁶ As of March 2017, the FDA has only approved two CM-manufactured products, one each for Vertex Pharmaceuticals and Janssen Pharmaceuticals. While more approvals are expected, there is very little real-world experience to help assess whether and to what extent expected cost reductions, quality improvements, and developments in manufacturing flexibility will be realized.

Pfizer's experience in its "hybrid" approach to CM technology adoption provides some perspective on what might be expected.¹⁷ Pfizer selectively adopted CM processes only for high-volume products and in selected drug manufacturing processes. The company's VP of Global Technology Services reported that despite engineering-driven CM cost advantages over batch manufacturing (e.g., higher throughput on a smaller footprint, no scale-up, greater flexibility, shorter lead times from raw material purchase to production of finished product), his company's actual experience with CM is that the business case for CM investment was not "durable," even for high-volume drugs like Lipitor. Marginal capital expenditure costs were included among the several factors he cited. While operating costs of CM may be lower, "[y]ou need high volume so that you are multiplying by a big number of units to realize value," the Pfizer VP said. "If you've got a batch facility that is largely depreciated, and you've got to build a new CM facility, you need to compare capital and operating costs in your analysis."

Based on experiences such as these, it would not be a surprise to see a lengthy transition in switching to CM, and significant organizational transition costs should be anticipated.

It takes some time to adapt and develop these applications. You start in a pilot environment to develop data that convinces you it will work. Then you develop data to convince regulators so they will approve it as an alternate process. These activities take several years to work through. In our case, some of the business cases changed during this time frame. Though the deployments were technically very successful and effective when installed for commercial manufacturing, some of the manufacturing sites are no longer in our network, and the products have gone generic. When we look at the costs to relocate that technology to another site, it really didn't have a good ROI.¹⁸

This perspective underscores an important issue for the application of CM to the generics business. If branded manufacturers with high-volume drugs are not able to capture sufficient cost savings from CM to make a reasonable business case for its adoption, it is highly likely that the application of CM in the generics industry,

¹⁵ Based on Indian labor costs (~87% of US on a productivity-adjusted basis), labor cost savings would be commensurately lower (\$139,200 per US-equivalent operator cost per year, 87% of the 50% labor cost savings, or 43.5%).

¹⁶ Eglovitch, *supra*, note 10.

¹⁷ Rob Wright, "Pfizer's Hybrid Approach to Implementing Continuous Manufacturing Processes," *Pharmaceutical Online*, Aug. 30, 2013, <http://www.pharmaceuticalonline.com/doc/pfizer-s-hybrid-approach-to-implementing-continuous-manufacturing-processes-0001>.

¹⁸ *Id.*

at least with the current state of technology, will be very limited. As discussed above, absent artificial barriers to entry, equilibrium profit margins on generic drugs will be very low. Even a product with a large share of a particular generic firm's sales would provide very little room to invest in changing manufacturing technology, particularly in the typical case when there is little guarantee that sales shares will remain stable over time. Moreover, if changing manufacturing technology brings with it increased regulatory uncertainty and cost,¹⁹ it is unlikely that generics companies will be able to undertake the transition in an economically efficient manner.

V. HOW LARGE IS THE COST OF TRANSITIONING TO CM?

As mentioned above, companies facing the possibility of adopting a new technology must compare the costs and benefits of abandoning existing technology and moving to the new. Evaluating the existing capital stock of companies in the pharmaceutical industry suggests that the abandonment cost is potentially very large. To justify incurring those costs, the benefits to the companies of making the change would have to be even larger.

V.A. The cost of abandoning existing manufacturing capacity

A key determinant of whether to adopt a new manufacturing technology is the cost of bringing new manufacturing equipment (capital) online, a figure specific to the new technology. Even if a new technology may result in lower manufacturing costs and/or higher quality, a company considering a change in manufacturing technology must compare the cost of continuing to use an existing process (which uses established capital equipment and known methods) to the costs and benefits of switching to a new technology and new methods. These costs and benefits will depend on the competitive structure of the market, regulatory conditions, and other key factors. This suggests that the path toward new manufacturing technologies may be quite different in the brand as opposed to the generics sector. When the new technology involves the abandonment of an existing plant and equipment, the lower cost of using existing capital can delay the adoption of a new technology in a highly competitive sector such as generic drugs.²⁰

It is notable that, despite the common view that CM processes are more efficient in the pharmaceutical industry, that perspective is not unchallenged. Industry experts argue that under certain circumstances, CM actually raises costs and produces less efficient output. For example, a company may need to produce relatively small amounts of product on a periodic basis to assure that its inventory has sufficient time before it expires. In that case, the setup cost, cleanup cost, and time associated with CM could be in excess of any gains achieved.

To get a sense of the transition costs involved in moving toward CM processes in the pharmaceutical industry, we can examine the size of the physical capital stock in pharmaceutical manufacturing generally and more specifically in the generics segment of the industry.

¹⁹ Despite the FDA's support for CM adoption, the process of implementing CM requires substantial interaction with the Agency and a nontrivial regulatory cost. At an FDA meeting discussing ways to advance product quality, a regulatory executive with a large pharmaceutical company was quoted as saying, "What I worry about with continuous manufacturing, because it is new and it is a little bit complicated to understand initially, is that if we don't start to think about this sooner we will wind up having multiple views of what continuous manufacturing is and we will be establishing different continuous manufacturing criteria" (Eglovitch, supra, note 10, p. 5). This same executive discussed the cost and complexity of inspection processes and a tremendous growth in information requirements. "When I started in regulatory in 1994 and I filed a CMC section around the world, this was about 1,000 pages of CMC information for a small molecule. There was about six volumes for a biologic. Now we are filing on the order of about eight or nine volumes for a small molecule and about 26 volumes for a biologic. That is a lot of additional information and data. This is creating a burden for all of us" (Eglovitch, supra, note 10, p. 7).

²⁰ For an analysis of how economic conditions influence the adoption of new manufacturing technology in a construction materials industry, see Jeffrey T. Macher, "Finding Mr. Schumpeter: An Empirical Study of Competition and Technology Adoption" (working paper, Georgetown University, 2017).

Unfortunately, it is impossible to directly observe the market value of manufacturing capital extant in any industry because such assets are not typically bought and sold in settings where such transactions are made public. As a proxy, however, we can measure the accounting (“book”) value of physical capital reported on the balance sheets of publicly traded companies in the pharmaceutical industry.

By that measure, existing manufacturing capacity is plentiful and long-lived. Moreover, average capacity utilization is not high.²¹ This means that the marginal cost to most companies in the pharmaceutical industry of utilizing existing manufacturing technologies is low. As illustrated in Figure 9, current physical assets of publicly traded companies in the pharmaceutical industry exceed \$400 billion on a gross basis, with a net value exceeding \$200 billion after depreciation. For large publicly traded generics companies, these amounts are approximately \$15 billion and \$25 billion, respectively (see Figure 11).²²

It is important to note that the fixed asset base of the larger pharmaceutical industry is not entirely dedicated to manufacturing, but for the generics sector, manufacturing occupies a large share of costs (roughly half of revenue). For a highly competitive industry with low operating margins, the cost of abandoning existing manufacturing capital is potentially a substantial barrier to adopting new technology.²³

Figure 9 – 2014 and 2015 gross and net fixed assets

Book Value of Assets, Publicly Traded Pharmaceutical companies. \$USD (billion)	2014		2015	
	Fixed Assets	Pct of Total for Companies Reporting	Fixed Assets	Pct of Total for Companies Reporting
Gross Property, Plant, and Equipment	\$407.85	100.0%	\$410.21	100.0%
• Machinery	\$210.46	51.9%	\$209.84	51.5%
• Buildings	\$107.11	36.4%	\$109.59	36.9%
• Land	\$43.53	12.1%	\$42.98	12.0%
• Construction in progress	\$35.48	9.1%	\$36.28	9.3%
Net Property, Plant, and Equipment	\$206.14	50.5%	\$210.03	51.2%

Source: S&P Capital IQ, NAICS Code 3254.

Note: Includes brand and generic companies, worldwide. NAICS Code 3254 (15,222 operating Pharmaceutical and Medicine Manufacture companies, worldwide, 604 with public data. No data available for private companies.

Source: S&P Capital IQ, NAICS Code 3254 Notes: Machinery, Buildings, Land and CIP total percentages may not sum to 100% because of missing sub-category data for some companies. Percentages for sub-categories are calculated as percent of Gross PPE for those companies with both sub-category and Gross PPE data reported. Includes brand and generic companies, worldwide. 15,222 operating Pharmaceutical and Medicine Manufacture companies, worldwide, 604 with public data. No data available for private companies.

Moreover, as illustrated in Figure 10, for those public companies reporting current year and accumulated depreciation and depreciable asset balances, depreciable assets were only approximately 54% depreciated. The

²¹ US pharmaceutical manufacturing capacity utilization was 63% in 2014 according to the US Census Bureau.

²² The values presented in Figure 11 represent those reported by the largest publicly traded traditional generics companies. They do not include the assets of the generic sub-divisions of large traditionally branded manufacturers, such as Novartis, Sanofi, and others that operate large generic drug businesses. Similarly, these numbers do not include the total assets of traditionally generic companies that also sell branded products. Public financials do not allocate assets across lines of business, so differentiating brand-related assets from generic-related assets is not possible. However, the generics businesses of large traditionally brand companies tend to be substantially larger than are the brand businesses of traditional generics companies. As a result, the data in the table represent a conservative statement of fixed assets associated with generics manufacturing.

²³ Note that company public filings indicate that for 2016, as a share of Revenue, Mylan reported Cost of Goods Sold (COGS), a proxy for manufacturing cost, equal to 57% and Net Income equal to 4%; Teva reported COGS of 46% and Net Income of 1.5%. For the three years 2014–2016, the 25 publicly traded generics manufacturers with the greatest sales reported COGS and Net Income as a percentage of Revenues were 47.4% and -1.3%. This underscored the competitive, low-profit nature of this sector.

average total lifespan of their depreciable assets was about 17 years, and the remaining lifespan of depreciable assets for these companies was about 8 years. As reported, depreciation percentages and asset lifespan are broadly similar for generics companies as for the entire sample of companies. This indicates that to the extent that the adoption of CM technologies requires the abandonment of existing equipment, that cost would be very large, particularly for generics companies.

Figure 10 – 2014 and 2015 lifespan of depreciable assets

Percent depreciated, lifespan and remaining life of depreciable assets	2014	2015
Depreciable assets (machinery and buildings)	\$254,328,345,000	\$257,320,089,000
Current year depreciation	\$15,099,068,000	\$15,052,849,000
Accumulated depreciation	\$138,034,711,000	\$138,120,431,000
Percent depreciated (depreciable assets)	54.3%	53.7%
Lifespan of depreciable assets (years)	17	17
Average remaining lifespan (depreciable assets)	8	8

Source: S&P Capital IQ, NAICS Code 3254

Notes: Includes only those companies with depreciable assets, current year depreciation, and accumulated depreciation data reported. Includes brand and generic companies, worldwide. 15,222 operating Pharmaceutical and Medicine Manufacture companies, worldwide, 604 with public data. No data are available for private companies.

Figure 11 – 2015 Gross and net fixed assets by company, by asset type: Largest generic drug manufacturers

Company	Gross PP&E	Net PP&E	Machinery	Buildings	Land	Current year depreciation	Percent depreciated	Average remaining lifespan
Allergan	N/A	N/A	N/A	N/A	N/A	\$128.60	N/A	N/A
Mylan	\$3,294.00	\$1,983.90	\$1,928.40	\$950.60	\$124.50	\$186.10	46%	8
			59%	29%	4%			
Par Pharmaceutical Companies Inc.	\$275.80	\$217.30	\$110.00	\$63.60	\$11.10	\$27.90	34%	4
			40%	23%	4%			
KrKadd Novo Mesto	\$1,922.30	\$897.30	\$1,032.40	\$818.30	N/A	\$108.10	55%	8
			54%	43%	2%			
StadaArzneimittel AG	\$642.60	\$319.10	\$356.00	N/A	N/A	\$37.20	N/A	N/A
			55%					
Aurobindo Pharma Limited	\$945.00	\$662.80	\$581.70	\$157.90	\$49.90	\$52.00	38%	9
			62%	17%	5%			
Cadila Healthcare Limited	\$784.70	\$550.60	\$456.30	\$133.90	\$26.10	\$42.60	40%	8
			58%	17%	3%			
Cipla Limited	\$1,306.30	\$809.80	\$802.10	\$368.30	\$23.80	\$76.90	42%	9
			61%	28%	2%			
Dr. Reddy's Laboratories Ltd.	N/A	N/A	N/A	N/A	N/A	\$102.30	N/A	N/A

cont.

Figure 11 – 2015 Gross and net fixed assets by company, by asset type: Largest generic drug manufacturers (cont.)

Company	Gross PP&E	Net PP&E	Machinery	Buildings	Land	Current year depreciation	Percent depreciated	Average remaining lifespan
Lupin Limited	\$991.30	\$640.30	\$595.10	\$185.80	\$47.40	\$61.00	45%	7
			60%	19%	5%			
Sun Pharmaceutical Industries Limited	\$2,436.20	\$1,321.70	\$1,487.20	\$675.00	\$60.50	\$152.90	52%	7
			61%	28%	2%			
Teva Pharmaceutical Industries Limited	\$9,548.00	\$6,019.00	\$6,563.00	\$2,591.00	N/A	\$468.00	39%	12
			69%	27%				
Valeant Pharmaceuticals International, Inc.	\$2,625.80	\$1,441.80	\$1,603.10	\$655.40	\$81.10	\$209.20	52%	5
			61%	25%	3%			
Nichi Iko Pharmaceutical Co. Ltd.	N/A	N/A	N/A	N/A	N/A	\$43.70	N/A	N/A
Aspen Pharmacare Holdings Limited	\$864.30	\$650.30	\$362.20	N/A	\$296.30	\$41.20	N/A	N/A
			42%		34%			
	\$25,636.30	\$15,513.90	\$15,877.40	\$6,599.80	\$720.80	\$1,737.80	44%	8
			62%	32%	4%			

Sources:

[A] Top 20 Generic Companies by 2014 Revenue, reported by FiercePharma. Source indicates top 20 generics companies accounted for 83.1% of worldwide generic drug revenues. FiercePharma relies on data from market intelligence firm Evaluate.

[B] Data reported in Tables are from Standard and Poor's Capital IQ Financial data.

Notes: Excludes Fresenius SE Co KGaA (Limited generic drug manufacturing except for parenterals), Apotex (Private Company: No financial data available), and Hospira (Pfizer injectables manufacturing division). Novartis (Sandoz) and Sanofi are also excluded.

Gross PPE: Gross book value of property, plant and equipment

Net PPE: Gross PPE less Accumulated Depreciation

VI. WHAT IS THE POTENTIAL FOR CM TO ENCOURAGE MANUFACTURING IN THE UNITED STATES?

In important 2013 congressional testimony, Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, stated that policies promoting CM technology would tend to favor US domestic manufacturing. Quoting Dr. Woodcock, "These new ways of making drugs could, with the proper strategies, revitalize pharmaceutical manufacturing in the United States."²⁴ Continuing, Dr. Woodcock suggested that the trend toward offshore drug manufacturing is related, at least in part, to the low labor cost of foreign manufacturing and

²⁴ Statement of Janet Woodcock, MD, before the Subcommittee on Energy Policy, Health Care and Entitlements, Dec. 12, 2013.

large footprint of historically dominant batch manufacturing technology. She stated, “While there are multiple reasons for this shift, common underlying factors include the fact that most traditional drug production processes require a large footprint, often have environmental liabilities, and can utilize a low-cost labor force.”²⁵

The economic reasoning implicit in pairing advocacy of policies to promote CM adoption and the prospect of reversing the trend toward offshoring appears to rest on two arguments: (1) CM is less labor-intensive than batch manufacturing; the prospect of lower-labor costs would provide a less compelling reason to locate drug manufacturing offshore if CM is more widely adopted. (2) Because CM facilities require a smaller footprint than batch facilities, the higher cost of real estate in the United States should be less of a competitive disadvantage if CM is more widely adopted.

The prospect of revitalizing US drug manufacturing is not necessarily restricted to new or greenfield drug manufacturing investments. In keeping with the current US administration’s call for policies promoting US manufacturing, interested parties may suggest that drug manufacturing might even return to the United States if FDA policy encourages CM.²⁶ Some may perceive this to be part of a general nascent “reshoring”²⁷ manufacturing trend, i.e., relocation of manufacturing from emerging economies like China to the United States. In this context, it is important to explore the drivers of manufacturing location and to assess the likelihood that CM will indeed contribute to a resurgence of US manufacturing in this sector.

One of the key issues related to offshore manufacturing is the FDA’s operational (and budgetary) challenge in inspecting offshore drug manufacturing facilities. A recent Government Accountability Office (GAO) report found that as of fiscal year 2017, approximately 60% of all drug manufacturing establishments that would be subject to FDA inspection are outside the United States. While through the first half of 2016, more foreign establishments had been inspected than domestic ones, but fully one-third of foreign establishments may never have been inspected (as opposed to 14% of US establishments). Moreover, the GAO reported that 46% of staff positions in FDA foreign offices are vacant. The GAO concluded that the FDA should address these all these issues and should assess the effectiveness of its foreign offices.²⁸ A return of manufacturing to the United States would certainly reduce the FDA’s inspection burden.

VI.A. The role of US manufacturing costs

Dr. Woodcock’s reference to low foreign labor costs is consistent with extensive research on factors that influence manufacturing facility location decisions. More automated manufacturing tends to favor US manufacturing, while less automated and routinized manufacturing is more likely to be located offshore. Academic meta-studies confirm that cost is generally the most important factor influencing global manufacturing location decisions and that labor cost is, in particular, usually the most important factor in manufacturing reshoring decisions.²⁹ However,

25 Note that company public filings indicate that for 2016, as a share of Revenue, Mylan reported Cost of Goods Sold (COGS), a proxy for manufacturing cost, equal to 57% and Net Income equal to 4%; Teva reported COGS of 46% and Net Income of 1.5%. For the three years 2014–2016, the 25 publicly traded generics manufacturers with the greatest sales reported COGS and Net Income as a percentage of Revenues were 47.4% and -1.3%. This underscored the competitive, low-profit nature of this sector.

26 As is the case for other industries, encouragement of more automated US manufacturing might reduce US manufacturing employment. Based on one published guesstimate that CM plants would require only half the direct labor of batch plants, and based on the number of production worker in NAICS 3254 in 2015, 66,000 US drug manufacturing production employee positions would be permanently eliminated. Schaber et al., *supra*, note 15.

27 Lydia Bals, Anika Daum, and Wendy Tate, “From Offshoring to Rightshoring: Focus on the Backshoring Phenomenon,” *Academy of International Business Insights*, 15, no. 4 (2016): 3–8.

28 US Government Accountability Office, “Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of its Foreign Offices” (GAO-17-143, Dec. 2016), available at <https://www.gao.gov/assets/690/681689.pdf>.

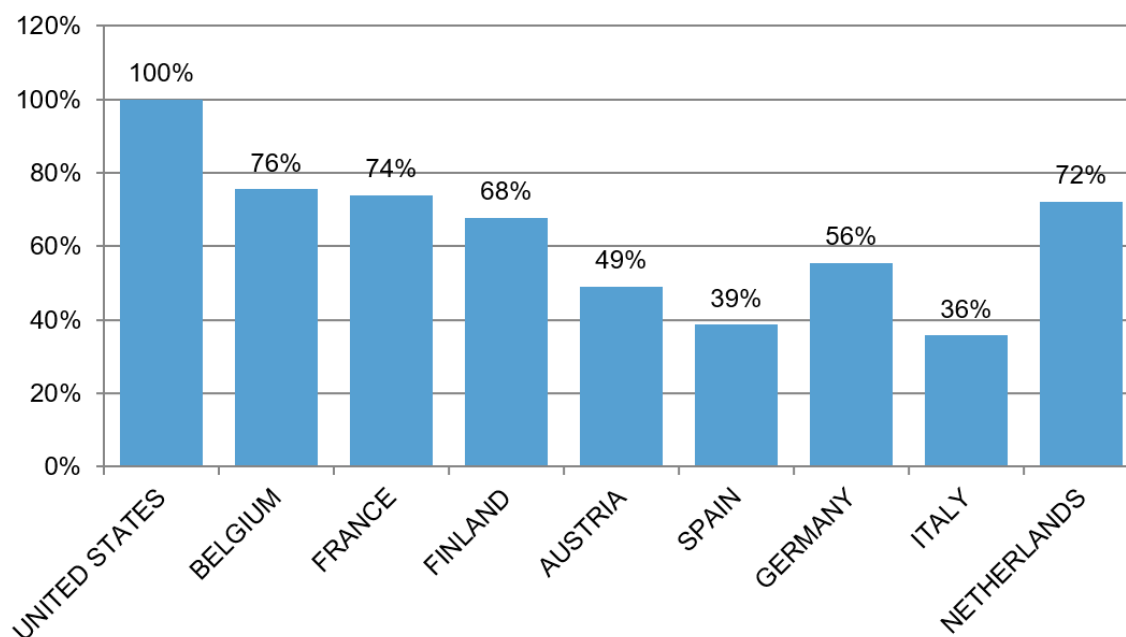
29 B.L. MacCarthy and W. Atthirawong, “Factors Affecting Location Decisions in International Operations—A Delphi Study,” *International Journal of Operations & Production Management* 23, no. 7, (2003): 794–818; and William White and Andrew S. Borchers, “Motivation Behind Reshoring Decisions in Manufacturing,” *Operations and Supply Chain Management* 9, no. 3 (2016): 205–09.

evidence suggests that the pharmaceutical industry does not necessarily conform to these more general findings.

VI.A.1. US productivity-adjusted manufacturing costs

Globally, manufacturing nominal wage rates and total labor costs tend to vary enormously, and are often lower outside the United States.³⁰ However, US manufacturing labor productivity is higher than in most countries, which tends to compensate for high US nominal-compensation costs. Figure 12 below shows that foreign manufacturing productivity is lower than in the United States, even in developed countries such as Germany, France, Belgium, and the Netherlands, all of which are large exporters of drugs to the United States.

Figure 12 – Countries' productivity relative to the United States, relative output per hour, 2013



Source: Conference Board, International Labor Comparisons, available at <https://www.conference-board.org/ilcprogram/>.

As a result, US manufacturing-labor costs tend to be surprisingly competitive.³¹ US manufacturing-cost competitiveness has also improved over the past 30 years, as other locations, especially China, dramatically lost ground.³²

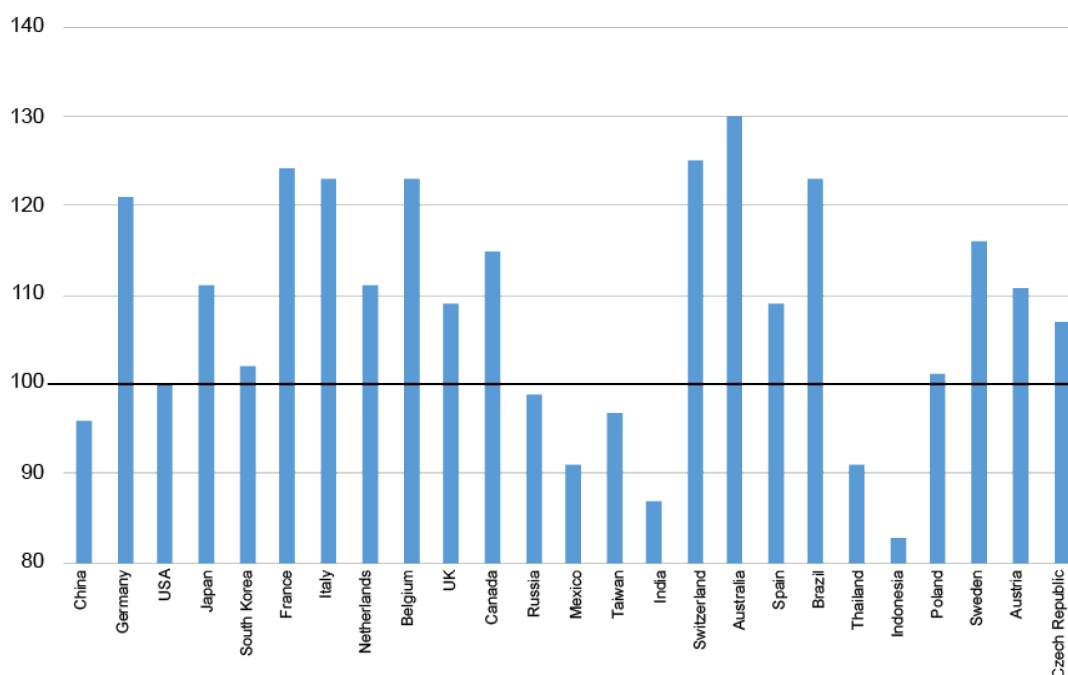
30 Harold L. Sirkin, Michael Zinser, and Justin Rose, "The Shifting Economics of Global Manufacturing: How Cost Competitiveness Is Changing Worldwide," The Boston Consulting Group, Aug. 19, 2014, available at https://www.bcgperspectives.com/content/articles/lean_manufacturing_globalization_shifting_economics_global_manufacturing/.

31 "Study: US Manufacturing Remains Most Competitive Worldwide Despite Headwinds," Quality Magazine, Mar. 15, 2016, reporting on a report by Oxford Economics, <http://www.qualitymag.com/articles/93183-study-us-manufacturing-remains-most-competitive-worldwide-despite-headwinds>; Janet Ceglowski and Stephen Golub, "Does China Still Have a Labor Cost Advantage?" Global Economy Journal 12, no. 3 (2012), available at http://repository.brynmawr.edu/cgi/viewcontent.cgi?article=1002&context=econ_pubs&sei-redir=1&referer=http%3A%2F%2Fscholar.google.com%2Fscholar%3Fhl%3Den%26q%3Ddoes%2Bchina%2Bstill%2Bhave%2Ba%2Blabor%2Bcost%2Badvantage%253F%26btnG%3D%26as_sdt%3D1%252C9%26as_sdt%3D#search=%22does%20china%20still%20have%20labor%20cost%20advantage%3F%22.

32 Numerous sources have documented the rapid rise in nominal wage rates in China and elsewhere. A typical finding is expressed in the following: "The reality of rising wages across China demonstrates that the country has already lost its once formidable comparative advantage as the world's lowest-cost manufacturer." Deloitte, "Competitiveness: Catching the Next Wave—China," September 2014, available at <https://www2.deloitte.com/content/dam/Deloitte/global/Documents/About-Deloitte/gx-china-competitiveness-report-web.pdf>.

Other evidence also suggests that the perception of prohibitively high manufacturing costs in the US relative to other countries may not be well founded. Figure 13 below compares 2014 US manufacturing cost competitiveness to that of 24 other major exporting countries, as reported by Boston Consulting Group (BCG). Relative to the United States, productivity-adjusted manufacturing costs in European countries, including Germany, Switzerland, Italy, France and Belgium, were about 20%–25% higher than those of the United States, the United Kingdom's were 9% higher, and Japan's were 11% higher. These countries were all major sources of US drug imports and/or had a large number of FDA-regulated foreign-drug facilities. BCG reported that manufacturing costs in China were lower than US costs, but on a productivity-adjusted basis, by only 4%. India's manufacturing costs were 13% lower than the United States'. In 2016, India ranked fourth and China ranked nineteenth in the dollar value of US drug and biotechnology medications imports.³³ India and China have nearly the same number of FDA-regulated drug-manufacturing facilities (ranked first and second, respectively), even though China's labor-cost advantage was smaller than India's.³⁴ On a productivity-adjusted basis, US manufacturing is increasingly cost competitive.

Figure 13 – Manufacturing cost index top 25 export economies, 2014



Ranked by volume of exports (high to low)

Source: BCG, "The Shifting Economics of Global Manufacturing." Available at: https://www.bcgperspectives.com/content/articles/lean_manufacturing_globalization_shifting_economics_global_manufacturing/

VI.A.2. Labor costs and related currency risk exposure

Since most foreign countries from which the US imports drugs have higher productivity-adjusted labor costs than the United States, labor cost disadvantages of moving CM plants to those countries should be less than under more labor-intensive batch processes. Reduced labor costs may also decrease currency-related risk exposures for multinational companies. Labor costs paid in local currency expose a foreign investor to risks it does not face

³³ Bates White calculations from US Bureau of Census data, available at <https://relatedparty.ftd.census.gov/>.

³⁴ Relative productivity adjusted cost reported by BCG confirm higher-than-US costs in Germany, Switzerland, Belgium, Italy, France, the United Kingdom, Canada, and Japan. Based on different data presentations from other sources, Ireland and Denmark are generally found to have relatively high labor costs compared with other European Union countries, all of which have higher productivity-adjusted labor costs than the United States. Singapore's productivity-adjusted labor costs are also higher than those in the United States. Ceglowski and Golub, supra, note 32, p. 16; and Rory O'Farrell, "Wages and Ireland's International Competitiveness," *Economic and Social Review* 46, no. 3 (2015): 429–58, <http://www.esr.ie/article/view/401>.

when producing in its home currency. For example, when a US-based multinational company pays its factory workers in local currency in Ireland (Euros), it bears risk that does not exist when paying its US-based factory workers. Research indicates that one of the two most important factors influencing manufacturing reshoring decisions is the importance of currency stability.³⁵

VI.B. US tax competitiveness

Ireland, Switzerland, and Singapore, which have highly competitive tax regimes, are three of the top ten countries from which the United States imports prescription drugs. These countries' statutory and marginal effective corporate tax rates are much lower than are those of other top-ten countries, as shown in the following table.³⁶ All are lower than the United States' pre-2018 40% statutory and 35.3% marginal rates.

Figure 14 – Statutory and marginal effective corporate tax rates, 2014

Country	Statutory corporate tax rate	Marginal effective tax rate
Ireland	12.5	10.2
Germany	29.6	24.4
Switzerland	17.9	17.5
Israel	26.5	16.1
UK	21.0	23.7
India	34.0	35.1
Canada	26.5	18.8
Denmark	24.5	18.6
Belgium	34.0	18.5
Singapore	17.0	9.2

Definitions

1. The statutory corporate tax rates represent the combined central and subcentral corporate income tax rates.
2. The marginal effective tax rate measures the tax liability expected to be incurred on an additional dollar of investment.

Source: Peterson Institute for International Economics, "Policy Brief: Lessons for US Business Tax Reform from International Tax Rates," January 2017.

Ireland, Switzerland, and, more recently, Singapore have historically been highly successful in attracting multinational-pharmaceutical company manufacturing, in part through their favorable tax policies. Economic research indicates that favorable tax law has not been the only factor favoring manufacturing employment in Ireland.³⁷ Skilled workforces, proximity to markets, and infrastructure advantages distinguish tax-competitive and other major drug-exporting countries as desirable locations for drug manufacturing.

³⁵ White and Borchers, *supra*, note 30.

³⁶ Most countries, also impose value-added taxes (VATs). Export sales to the United States or elsewhere are not subject to VATs.

³⁷ "This is not to say that tax rates are solely responsible for the large volume of foreign direct investment in Ireland. Approximately forty countries offer near-blanket tax exemptions for foreign investors, yet few of these have experienced the influx of foreign direct investment of the magnitude of Ireland." James R. Hines, "Sensible Tax Policies in Open Economies," *Dublin: Journal of the Statistical & Social Inquiry Society of Ireland*, XXXIII (2003/2004): 1–39.

Puerto Rico's history of favorable tax treatment illustrates that while tax incentives may initially influence manufacturing location decisions, tax alone does not dictate drug manufacturing location and plant investment decisions. Until 1996, under Internal Revenue Code Section 936, income derived from locating manufacturing in Puerto Rico was generally exempt from US federal corporate taxation. Despite the repeal and phase out of IRC 936 incentives,³⁸ Puerto Rico continues to house more facilities and employ substantially more pharmaceutical workers than Ireland, in part because of its skilled workforce and the sizeable stock of existing manufacturing capacity.

The United States enacted new tax legislation (informally called the Tax Cuts and Jobs Act) on December 22, 2017, which includes fundamentally new international tax provisions. The new tax law features a globally competitive 21% corporate tax rate, even lower rates for income derived from US exports and for income derived on certain foreign investments by US-headquartered multinationals, immediate expensing of US capital expenditures and several anti-abuse provisions. The ostensible purpose of these provisions is to discourage tax-motivated offshoring of manufacturing and other business investments. As the Internal Revenue Service and Treasury begin the arduous, years-long process of revising numerous tax regulations, notices, revenue procedures, and other hard and soft guidance implementing the new tax law, there is considerable uncertainty about the likely impacts of these new international tax rules. Certain complex provisions of and interactions among the new Global Low Tax Intangible Income, Foreign Derived Intangible Income, and Base Erosion and Anti-Abuse taxes may ironically incentivize off-shoring of manufacturing to lower-tax jurisdictions.³⁹ Foreign tax authority responses to these US tax initiatives is also difficult to predict. In some cases, foreign governments have or are expected to react to the new US law by proposing even more attractive rates and competitive retention and new investment inducements.⁴⁰

VI.C. Construction costs

There also does not appear to be a convincing case for a return to domestic manufacturing based on footprint-related cost considerations, as suggested by the FDA. As shown in Figure 15, among the top ten countries from which US drug imports are highest (in dollar value) for which we have data on construction costs, those costs are lower than in the United States in five countries and higher in the other five. Among the lower construction cost countries is Ireland, which has already been the site of substantial multinational company CM investment. Pfizer manufactures Lipitor in Cork County, Ireland. The company introduced CM processes to manufacture Lipitor in Ireland, in part because it was such a high-volume product.⁴¹ Building new CM facilities in any of these five countries, particularly in tax-advantaged Ireland, would appear to result in lower construction-related costs.⁴²

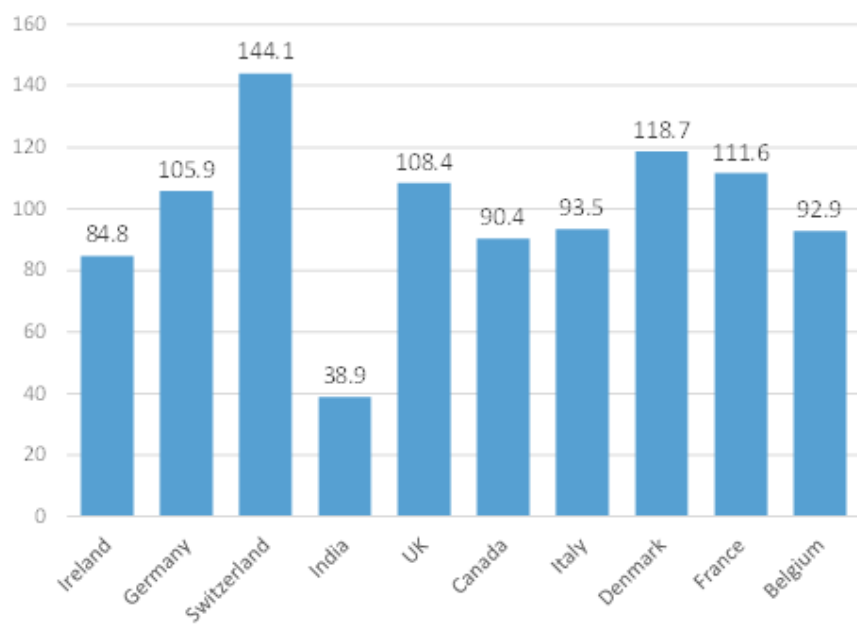
38 Louis Garguilo, "Puerto Rico Back on the Map of Pharmaceutical Locations," *Outsourced Pharma*, July 24, 2014, available at <https://www.outsourcedpharma.com/doc/puerto-rico-back-on-the-map-of-pharmaceutical-locations-0001>.

39 Deloitte, "Tax Reform Ushers in a Raft of International Tax Considerations," *Wall Street Journal*, Dec. 22, 2017; Lee Sheppard, "International Clawbacks and Minimum Taxes In Tax Reform," *Tax Notes*, Dec. 29, 2017; "GILTI May Entice Low-Margin Businesses to Move Abroad," *Tax Notes*, Dec. 20, 2017; Natalie Kitroeff, "Tax Law May Send Factories and Jobs Abroad, Critics Say," *New York Times*, Jan. 8, 2018.

40 "Pressure Builds for Swiss Tax Reform After US Cuts," *BNA Transfer Pricing Reporter*, Jan. 9, 2018; Alexandra Stevenson and Jack Ewing, "US Tax Bill May Inspire Cuts Globally, While Stirring Trade Tensions," *New York Times*, Dec. 22, 2017.

41 Eric Sagonowsky, "Pfizer Makes It Official, It Has Reversed Its Decision to Close Irish Lipitor Plant," *FiercePharma*, Mar. 11, 2015, available at <http://www.fiercepharma.com/supply-chain/pfizer-makes-it-official-it-has-reversed-its-decision-to-close-irish-lipitor-plant>. "Shortly after we had developed and implemented the CM process for these [Lipitor and Geodon] drugs, our analysis was no longer valid because the benchmark had shifted from internal [past high volume] to external [lower volumes following generic entry]." Pfizer nearly closed the Cork County plant, and planned to move production to Puerto Rico. Wright, *supra*, note 18.

42 Based on the asset data, land value represents only 4% of the gross book value of drug manufacturing assets for major generic drug producers. Minimizing land-related footprint costs would thus not appear to a primary driver of location decisions, foreign or domestic.

Figure 15 – Construction Cost Index, 2014

Source: International Construction Intelligence, 2014, Faithful & Gould, <https://www.fgould.com/americas/articles/international-construction-intelligence-usbase-14/>.

VII. POLICY IMPLICATIONS AND CONCLUSIONS

Advancing technology in pharmaceutical manufacturing is widely believed to have the potential to lower the cost of manufacturing and potentially increase quality and reliability of product supply. However, there are several reasons why manufacturing in this sector has not advanced as rapidly as it has in others. It is important that policy makers and other stakeholders take into consideration the challenges facing manufacturers as they consider the investment necessary to adopt new manufacturing technologies. It is also important that they understand and account for crucial differences between brand and generic drug manufacturers and how policies to encourage (or require) the adoption of CM technologies may impact the two sectors and potentially lead to undesirable effects.

Several of the issues discussed above suggest that the transition to CM has the potential to disadvantage generics companies—particularly smaller ones—and to lead to a less competitive market for generic drugs. If this were to be the result of policies that encourage the adoption of CM, it would likely exacerbate concerns about shortages and prices in the generics sector.

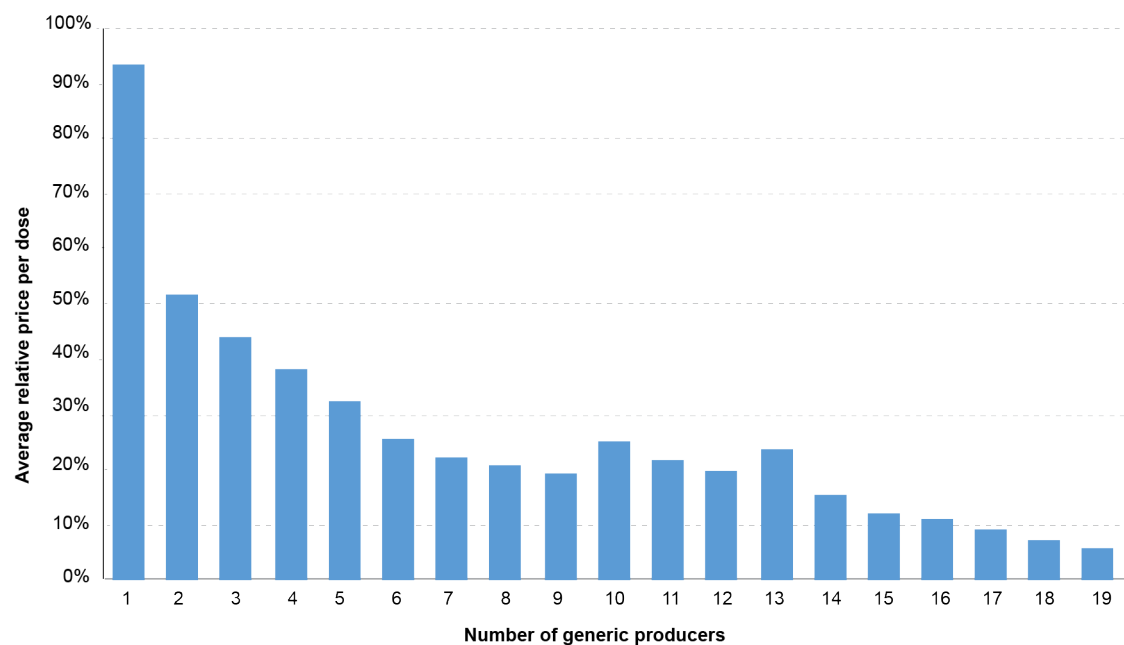
Beyond the basic economic principle that dictates that greater competition leads to lower prices, it is well established empirically that prices of generic drugs fall with greater entry and competition. Figure 16 below provides a chart produced by the FDA illustrating the strong inverse relationship between the number of entrants in generics markets and prevailing prices. The FTC has also published findings that the speed and depth of price decline in generic drug markets are both greater when there are more manufacturers competing to sell the product.⁴³ Policies or regulatory review practices that limit entry of products that are not continuously

⁴³ Luke M. Olson and Brett W. Wendling, "The Effect of Generic Drug Competition on Generic Drug Prices During the Hatch-Waxman 180-Day Exclusivity Period" (FTC Working Paper no. 307, April 2013).

manufactured are almost certain to result in higher rather than lower prices and with fewer competing companies, shortages will be more, not less, likely.⁴⁴

Many more details in the manufacturing process that have implications for the competitiveness of the generics sector need to be considered. For example, CM processes may require unique raw materials for production processes. The effects on upstream market structure of these markets (including Active Pharmaceutical Ingredient and excipient manufacturing) may result in higher raw materials and other input costs, which stand to work against the lower manufacturing costs achieved through CM processes. There are also organizational costs to consider, such as the need for greater coordination among raw material suppliers, equipment, and analytical instrument makers in early stages of product development. Especially in the current era of extreme price pressure, new pricing measures at the state and federal level, and purchaser consolidation, these increased costs may not be tenable.

Figure 16 – Generic drug prices tend to be higher when there are fewer suppliers



Source: FDA analysis of retail sales data from IMS Health, available at: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm>.

Moreover, as discussed above, there is a great deal of manufacturing capital already in use, with substantial economic life remaining. This indicates that the marginal cost of ongoing manufacturing and product development with existing (batch) technology is small. The gain of investing in new technology must be large to offset those costs. Branded companies have a limited window during which to gain the return from their investment. Unless the technology is already in place during the discovery and development phase, it is unlikely that a company will find it profitable to change techniques toward CM once its product is approved.

It is essential to understand that regulations serve to assure high-quality manufacturing, but also by their nature inhibit the adoption of new technology. Having received approval for a given process and location, the investment in developing new processes and waiting for new regulatory review imposes a cost that would be

⁴⁴ See, in addition, the research by Berndt et al. that demonstrates this reality, referenced in note 7.

uneconomic for many companies. This is more likely to be a concern for generics companies whose low margins make it harder to adjust to higher cost. As mentioned above (see note 6), the first FDA approved switch from batch to CM took five years to accomplish. So unless quantities and cost savings are quite substantial, there is little likelihood that it would be economically sensible for generics companies to invest in changing established and stable manufacturing techniques.

During development, generics companies are uncertain about the size of their potential market, time needed to gain approval, and whether they will have any exclusivity after approval. They also anticipate relatively limited time periods before competition or new innovation drastically reduces their opportunity to sell their product. This means that the larger upfront investment needed for continuous manufacturing may not be economically justifiable. If factors like a different impurity profile of a continuously manufactured brand prevent approval of a batch manufactured generic, this may mean that the market never realizes the substantial increases in cost savings and access provided by generics. This constrained market may also mean more economic pressure on the generics industry, exacerbating the risk of shortages.

The bottom line is that while there are interesting and potentially valuable improvements in pharmaceutical manufacturing being explored inside many companies and academic research centers, it is an easy mistake to focus the benefits without fully recognizing the potential complications. Policy makers and thought leaders should consider both the benefits and the costs involved in adopting continuous manufacturing. Companies generally have an incentive to choose the manufacturing methods that help them meet cost and profitability objectives and will be moved by competitive forces to make choices efficiently over time. Those forces operate within the pharmaceutical industry, but they are also intertwined with regulatory issues that complicate matters significantly. As policy makers consider opportunities to foster progress in pharmaceutical manufacturing, they should pay careful attention to the potential for unintended consequences that exacerbate, rather than address, the issues that concern patients and manufactures alike.

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