A Comparative Risk & Financial Analysis of Batch and Continuous Pharmaceutical Manufacturing Technologies

Implications for Strengthening U.S. Competitiveness & Supply Chains

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Executive Summary[1]

Maintaining a continuous supply of safe and effective, affordable pharmaceutical products, particularly those defined as "essential medicines" by the Food and Drug Administration (FDA), is a national imperative for U.S. consumers and the healthcare industry.[2] For the most part, pharmaceutical products consumed in the U.S. have adhered to these expectations. However, considerable reliance on foreign pharmaceutical manufacturing and dependence on decades old batch processing technology pose a number of risks to the pharmaceutical industry and consumers that raise serious concerns regarding the uninterrupted delivery of high-quality pharmaceutical products. The Covid-19 pandemic further laid bare the vulnerability of the U.S. pharmaceutical supply chain to unexpected events.

This study examines the risks and economics associated with investing in continuous (CM) versus conventional batch manufacturing for production of oral solid dosage pharmaceutical (OSD) products in the U.S. and abroad. Advanced technologies such as CM have gained interest in recent years based in part on their potential to reduce manufacturing costs by continuously processing inputs and materials throughout the development process. By contrast, batch processing is characterized by a sequence of steps that as described in more detail later can be inefficient and prone to more manual errors due to that technology's more labor-intensive approach. Continuous manufacturing is an advanced technology that was selected for this analysis based on growing industry and FDA interest in the evaluation of such capabilities for OSD products and where detailed cost information was available for empirical analysis.

In the most comprehensive financial analysis yet undertaken on CM manufacturing, a stochastic net present value (NPV) simulation of brand and generic manufacturing for new facilities is conducted comparing batch and continuous manufacturing processes leveraging actual industry financial revenue and cost information, and detailed engineering cost information of batch and CM manufacturing processes from a seminal manufacturing cost analysis of these two technologies. For each of the 156 different domestic and foreign manufacturing scenarios examined, the model generated 10,000 different NPVs from which a distribution of NPVs was generated. The major findings from this study are as follows:

- In the U.S., CM processes in almost all circumstances for both brand and generic companies result in higher NPVs than batch manufacturing processes, even under conservative CM cost volatility scenarios.
- Under current U.S. corporate tax rates, expected NPV of U.S.-based batch processing facilities is greater than that from investing in batch processing facilities in either China

[1] This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [FAIN] U01FD005946 totaling $285,000 with 100 percent funded by FDA/HHS. The contents are those of the author and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, the U.S. Government, CERSI or the University of Maryland.
[2] Stephen M. Hahn, Food and Drug Administration, FDA Publishes List of Essential Medicines, Medical Countermeasures, Critical Inputs Required by Executive Order, FDA Statement, October 30, 2020.

or India for both brand and generic companies but not when compared to Ireland due to that country's much lower corporate tax rate.

- Investing in CM technology in the U.S. under current corporate tax rates generates higher NPV than batch processes in China or India for both brand and generic companies. If U.S. corporate tax rates increase from 21% to 28%, it lowers expected net NPV for U.S. CM manufacturing investments.

Results indicate that continuous manufacturing has the potential to make manufacturing of OSD pharmaceuticals more economically attractive in the U.S. than foreign manufacturing of those products. The finding that batch manufacturing of OSD products in the U.S. is economically more attractive than investing in batch processes in China or India is driven by a combination of factors including competitive corporate tax rates and nonmanufacturing hedging costs that appear to already favor pharmaceutical manufacturing investments more broadly in the US and would be further enhanced by investment in lower cost CM technology. However, there is no indication that the industry has refocused much of their manufacturing investments toward the U.S. This raises serious questions regarding barriers and/or risks that may be preventing these companies from adopting advanced technologies for U.S. pharmaceutical manufacturing.

Factors likely to be driving a lack of investment in CM pharmaceutical manufacturing technology in the U.S. include the following:

- Lack of solid data on CM investment and operating costs that raises investment uncertainty.
- Potential management bias toward proven technology
- Manufacturing overcapacity
- Relative high cost of plant retrofitting due to large amounts of undepreciated manufacturing assets
- Potential lack of skilled labor to operate advanced manufacturing technology
- Market factors that favor greater focus on R&D investment over manufacturing investment
- Regulatory uncertainty regarding product approval leveraging advanced manufacturing processes
- More stringent environmental regulations in the U.S.
- Differential corporate tax rates between the U.S. and other countries
- A large percentage of API manufacturing outside the U.S. that can affect finished dosage form end products due to supply chain logistics

It will not be sufficient to merely demonstrate financial feasibility of advanced manufacturing technologies in order to induce the use of CM in the U.S. given long standing industry structural, economic and attitudinal issues that have dampened interest in adopting advanced manufacturing technology in the industry thus far. Crafting public policies to address such industry barriers and risks to domestic and advanced technology pharmaceutical manufacturing investment will be essential in ultimately stimulating such investments.

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Overview[3]

The provision of a continuous supply of affordable, safe and effective pharmaceutical products, particularly those defined as "essential medicines" by the Food and Drug Administration (FDA) is a national imperative as evidenced by one of the first executive orders of the Biden Administration to strengthen domestic supply chains.[4] For the most part, pharmaceutical products consumed in the U.S. have adhered to these expectations. However, considerable reliance on foreign pharmaceutical manufacturing that depends predominately on decades-old batch processing technology that is less automated and more difficult to scale production quickly raises serious concerns regarding the uninterrupted delivery of high-quality pharmaceutical products in the future. As of 2020, 74% of all active pharmaceutical ingredients (APIs) and 54% of all finished dosage form (FDF) human drug products were manufactured at facilities outside the U.S.[5]

A recall of the widely used blood thinning drug, Heparin in 2008 occurred due to an adulteration of the manufacturing process that introduced oversulfated chondroitin sulfate (OSCS) into batches of the product from a manufacturing facility in China and led to a large number of severe reactions to Heparin in the U.S. and some deaths. While an isolated event, considering the vast numbers of OSD products manufactured each year, the Heparin recall stands out as a cautionary tale for the importance of quality in pharmaceutical production.

Another persistent issue for the industry and the FDA has been drug shortages. Between 2013-2020, a total of 327 new shortages of drugs occurred and over the same period there were 553 ongoing drug shortages.[6] Casting additional light on the drug shortage issue was the COVID-19 pandemic which exposed shortages on 45 percent of the critical drugs used to combat the virus.[7]

The U.S. Cybersecurity and Information Security Agency (CISA) has designated a number of industries as Critical Manufacturing Sectors deemed essential to the functioning of the U.S. economy. Pharmaceuticals are not listed as one of those sectors. Nevertheless, a significant reliance on foreign manufacturing of pharmaceutical products increases the risk of destabilizing the U.S. drug supply chain due to geopolitical and other forces and thus poses a long-term threat to U.S. consumers.

This study examines the causes, risks and financial circumstances associated with offshoring pharmaceutical manufacturing of brand and generic products from the US along with analysis of

[3] I would like to thank Poulami Ghosh, Kai Xu, and Heng Zhuang for their excellent technical support and analysis and Mary Bittle Teer-Koenick for her project management support.
[4] The White House, Executive Order on America's Supply Chains, February 24, 2021. Stephen M. Hahn, Food and Drug Administration, FDA Publishes List of Essential Medicines, Medical Countermeasures, Critical Inputs Required by Executive Order, FDA Statement, October 30, 2020.
[5] U.S. Government Accountability Office, Testimony before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations, House of Representatives, Statement of Mary Denigan-Macauley, Director, Health Care, DRUG SAFETY FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog, 2020.
[6] FDA, Report to Congress, Drug Shortages for CY 2020, 2021.
[7] COVID-19: The CIDRAP Viewpoint October 21, 2020, Part 6: Ensuring a Resilient US Prescription Drug Supply.

how advanced manufacturing technology such as continuous manufacturing (CM) could become a catalyst for a U.S. renaissance in pharmaceutical manufacturing. For decades, the pharmaceutical industry has relied on batch processing in the manufacture of OSD drug products. Advanced technologies such as CM have gained interest in recent years based in part on their potential to reduce manufacturing costs by continuously processing inputs and materials throughout the development process. By contrast, batch processing is characterized by a sequence of steps that as described in more detail later can be inefficient and prone to more manual errors due to its more labor-intensive approach.

The pharmaceutical industry is characterized by divergent approaches to leveraging advanced technologies in R&D and manufacturing segments of the business. Research and development activities in the pharmaceutical industry have driven remarkable advances in new drug products including biopharmaceuticals most recently evidenced by the stunning introduction of mRNA Covid vaccines. These products illustrate the industry's quick adoption of advanced science in pharmaceutical R&D. Juxtaposed against pharmaceutical R&D is a general tendency for the pharma industry's investment to lag in advanced manufacturing technologies. Drivers of this dichotomous technology investment strategy for the industry include a strong bias toward processes with longer industry track records and low-cost manufacturing solutions. Advanced manufacturing technologies such as CM have been implemented in only a small number of sites and thus the industry has had far less experience with that technology's performance and cost than standard batch technology that exists at most manufacturing sites today in the U.S. and abroad.

A major contributing factor to pharmaceutical manufacturing outsourcing over the years includes a bifurcation between the brand and generic product markets where companies producing brand drugs enjoy product exclusivity over a long period of time that facilitates higher and more stable profit margins for that market segment compared to generic companies. The loss of exclusivity (LOE) poses much stiffer competition and an acute cost consciousness by generic companies faced with slimmer profit margins and greater sales volatility. For generics in particular, this market environment incents least cost manufacturing subject to FDA requirements on current good manufacturing practices (CGMP). Reinforcing this tendency have been the combined forces of increased scrutiny on drug pricing by policymakers and the consolidation and aggregation of pharmaceutical group purchasing organizations (GPOs) that create headwinds for pharma product pricing. Industry specialization in R&D and manufacturing has been facilitated by contract research organizations (CROs) and contract manufacturing organizations (CMOs) over the years which underscores the cost-driven nature of this sector.

Other factors at play in determining whether to manufacture pharmaceutical products in the U.S. or abroad include corporate taxes, differential labor and manufacturing costs, regulatory and environmental costs and foreign exchange hedging expense. Differential costs of production have been widely referenced as a primary reason for the loss of U.S. manufacturing over the last several decades. The ascendancy of China as a major manufacturing hub over the years was accomplished in large measure by much lower labor, land, and capital costs as well as more relaxed environmental regulations. Wage and cost pressures over time, however, have reduced

the China cost advantage in recent years to a slim 4% lower cost of manufacturing compared to the U.S.[8] This shift in overall manufacturing competitiveness along with the potential of more automated technologies such as CM that require smaller plant footprints could encourage more pharmaceutical manufacturing in the U.S. Alternatively, a more skilled labor force may be required to operate a CM facility which could lead to higher unit wage costs and training expenses initially. This analysis does not attempt to take these market dynamics into account due to a lack of data on this aspect of manufacturing cost.

Differential corporate tax rates are an important consideration by companies deciding whether and where to make a capital investment such as a manufacturing facility. In 2017, the Tax Cuts and Jobs Act reduced the U.S. marginal corporate tax rate from 35% to 21%. This change put the U.S. in a more tax favorable position compared with China and India, for example, that impose corporate tax rates of 25% and 30%, respectively.[9] Consequently, understanding the sensitivity of investment in manufacturing facilities in the U.S. and overseas to potential changes in U.S. tax policy in light of new proposals to raise corporate tax rates is critical to developing a complete picture of the dynamics of the manufacturing investment problem.

Regulation and environmental factors weigh in as additional nonfinancial considerations when selecting a manufacturing location. Inspection and oversight of pharmaceutical manufacturing is the responsibility of FDA. In 2019, the FDA conducted 1,258 Drug Quality Surveillance inspections.[10] FDA conducts these inspections on a periodic basis using a risk-based methodology where facilities indicating a potential for higher risk are inspected more frequently. Costs associated with noncompliance of CGMP depend on the severity and frequency of the issue and include forcing companies to perform costly remediation of quality deficient processes, a potential for drug recalls, civil money penalties and fines, and profit garnishments, among others.[11]The geographic distribution of facilities worldwide and limited staffing levels of FDA inspectors, along with country disparities in quality manufacturing also pose long-term challenges for the agency. In addition to CGMP and other FDA regulations, environmental regulations in the U.S. tend to be more restrictive than in other parts of the world, including some large pharmaceutical manufacturing countries. These regulations can extend timelines for when manufacturing sites can commence operation, impose additional costs associated with the required use of environmentally friendly equipment, specify special training and requirements for disposal of chemicals and solvents used in the manufacturing process as well as levy penalties for an environmental hazard.

[8] A Manufacturing Strategy Built for Trade Instability, Justin Rose, Ian Colotla, Michael MacAdoo, and Will Kletter, BCG, February 13, 2020.
[9] Elke Asen, Corporate Tax Rates Around the World, 2020, Tax Foundation, December 9, 2020.
[10] FDA, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Report on the State of Pharmaceutical Quality: Fiscal Year 2019, 2019.
[11] *21* Code of Federal Regulations *(*CFR*) Parts 210 and 211,* Title 21 – Food and Drug Administration, Department of Health and Human Services, Subchapter C – Drugs: General. Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs.

In addition to examining these drivers of pharmaceutical manufacturing, this study compares the net present value of new construction of continuous manufacturing facilities to new construction of batch manufacturing facilities for brand and generic companies operating in the U.S. and in select countries with large pharmaceutical manufacturing operations. Several hypotheses tested in the investment model are as follows:

- CM technology should generate higher NPVs than batch processing for brand companies in the U.S. due to higher and more stable profit margins making investments in such advanced technology economically attractive.
- Generic companies, due to less stable and lower profit margins, may find batch processing to be a more economically attractive U.S. manufacturing strategy.
- Investment in foreign batch manufacturing facilities may be more financially attractive than investment in U.S. batch manufacturing facilities due to lower costs abroad.
- Investment in CM manufacturing for brand companies at U.S.-based manufacturing facilities may be financially more attractive than investment in foreign manufacturing sites that rely on batch processing due to lower operating costs of CM even taking into account cost uncertainty with that technology.

A stochastic simulation of brand and generic manufacturing net present value (NPV) is performed. Operating and capital investment costs from a seminal engineering cost study comparing continuous and batch pharmaceutical manufacturing processes were used in the analysis along with historical revenues and other inputs of brand and generic pharmaceutical companies.[12] Revenues, operating, and capital costs were assumed to be stochastic variables in the model in order to develop a pharmaceutical manufacturing NPV distribution that examined expected NPV as well as probabilistically more extreme outcomes. More than 150 scenarios were tested among variations in manufacturing location (U.S., China, India, Ireland), product type (brand, generic), profit margin, foreign exchange hedge cost, operating and capital cost volatility with 10,000 simulations conducted per scenario.

The results from the study indicate that in the U.S., CM processes in almost all circumstances for both brand and generic companies result in higher NPVs than batch manufacturing processes, even under conservative CM cost volatility scenarios. U.S. CM process scenarios generate higher NPVs than batch processing scenarios in China and India for the majority of scenarios. Only in Ireland, which enjoys a significantly lower corporate tax rate (12.5%) than the U.S., does CM underperform batch manufacturing in terms of NPV along most scenarios. The results suggest that investment in CM processes in the U.S. by both brand and generic companies would not only result in higher NPVs over standard batch processing in the U.S. but result in higher NPVs over those associated with new batch facilities in either China or India under current U.S. corporate tax rates.

[12] For the historical financial performance analysis, brand and generic companies are defined by the Wharton Research Data Services (WRDS) as firms predominately focused on production and sale of these products.

The results of these simulations, however, do not explain the industry's relatively slow adoption of CM technology in OSD manufacturing. On one hand, the results for brand companies are entirely consistent with the composition of firms that have engaged with the FDA's Emerging Technology Program (ETP) to develop CM-based manufacturing capabilities. The firms involved in this program tend to be large brand producing companies. Other factors must explain why generic and brand companies overall are not yet attracted to CM technology investment at any scale of operation given the results of this study. Part of the answer appears to be due to significant embedded costs of existing batch technology investments reflected in large undepreciated accounts. Retrofitting existing manufacturing facilities to CM-based operations would add substantial near-term costs that over the long-run with depreciation would become more attractive financially. Other factors may include a lack of advanced skill sets and/or experience with CM technology along with cost and regulatory uncertainty. The latter issue is outside the scope of this analysis due to a lack of available information to reliably assess their impact on CM technology investment. However, cost uncertainty associated with CM manufacturing is incorporated in the simulation analysis via a set of stochastic cost variables.

From a public policy perspective, a number of factors warrant consideration as to whether and to what extent incentives for advanced manufacturing technologies should be provided to the pharmaceutical industry. President Biden signed an Executive Order on America's Supply Chains on February 24, 2021, calling on agencies to review the risks associated with certain designated critical supply chains including those for pharmaceuticals. Included in this Executive Order is a review of public and private incentives to encourage investment in production of "critical goods and materials." National interest or national security issues have been cited as reasons why certain industries or products merit some form of protection by way of risk mitigation strategies, information/research advantages or financial and/or tax incentives, among others. In the case of pharmaceutical manufacturing, an argument could be made for a policy aimed at raising the level of domestic production of pharmaceuticals in the U.S. through a variety of financial and nonfinancial measures. These could range from acceleration of private-public partnerships to serve as manufacturing labs for testing the feasibility of CM processes, and cost assessment, broadening access to federal technology resources and reducing regulatory requirements to the industry for accelerating CM development, to direct and indirect subsidies such as tax credits for eligible companies. Tradeoffs to consider in deciding what policy prescriptions should be leveraged include identifying root causes for the relative lack of industry investment, and the potential need for direct or indirect financial and nonfinancial support. Addressing domestic manufacturing with industrial policies that are designed to facilitate growth in some sector of production due to some observed or perceived market failure has been subject to much debate among economists over the years. Much of the criticism argues that government intervention in this case creates market inefficiencies and distortions that are better left to market forces to determine. Nevertheless, identifying industry barriers to domestic and advanced technology pharmaceutical manufacturing investment will at least help establish what type of policies may be most effective at stimulating such investments.

Pharmaceutical Industry Market Structure and Implications for Manufacturing Investment

Keys to understanding manufacturing investment decisions in the pharmaceutical industry lie in the market structure of this sector. For decades, a combination of regulatory policy, product segment bifurcation, healthcare public policy and market globalization factors have shaped the composition of the industry and consequently how it manufactures pharmaceutical products. Defining the pharmaceutical industry by its major product types helps first frame and focus this discussion. From an FDA perspective, medical products and manufacturing facilities regulated by the agency can generally be classified into three major types; medical devices; biologics, and drugs. Medical devices include any instrument or machine developed to diagnose, mitigate, or treat a disease or disorder. Given the nature of these products, their manufacturing process is quite different from biologics or drugs. Biologics are a broad class of product that are characterized by large complex molecules where development may occur using biotechnology or other advanced scientific methods. Vaccines, gene therapy and recombinant therapeutic proteins are just some examples of these types of products.[13] The third class; drug products serve as the focus of this study due to their ubiquitous market presence, scale and attention by FDA regarding the applicability of advanced technology for manufacturing of these products. Table 1 presents data on the total dollars of imported and exported FDA-regulated drugs by type in 2020.

Table 1 Total Imports and Exports of FDA-Regulated Products, 2020[14]

Product Type	Total Imports & Exports ($B)
Biologics	$67.8
Drugs*	$125.3
Devices	$126.8

*Total imports and exports for human and animal drugs

Drug products can further be segmented into the following forms: solids, liquids and other. Solid form drugs comprise products that typically come in capsule or tablet form. Liquids include parenteral products used to deliver a drug product through an intravenous injection in a sterilized environment or via an oral form. Other drug products include inhalants, topicals, sprays and suppositories. Today, approximately 60% of all drug products come in OSD form.[15]

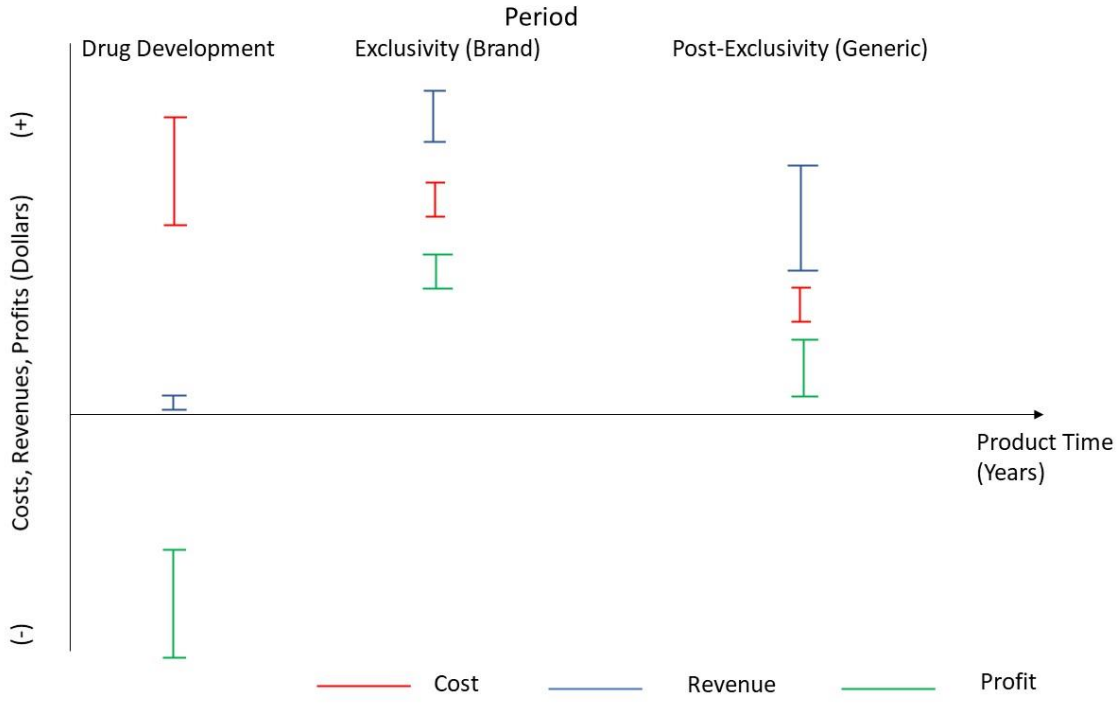
From a product branding perspective, pharmaceutical products are classified into brands or generics. This differentiation serves as a major driver of the market landscape seen in the

[13] FDA, "What Are Biologics Questions and Answers," February 6, 2018.
[14] FDA, Fact Sheet: FDA at a Glance, November 2020.

[15] Pharma Trends, The Reign of Oral Solid Dosage Forms in the Era of Biopharmaceuticals, March 30, 2020.

industry today. The product lifecycle shown in Figure 1 of a pharmaceutical product follows three major phases; development; brand period; and loss of exclusivity (generic). During the development phase, significant upfront investments and costs with considerable uncertainty are incurred in the research and discovery of a viable drug. Compared with other industries, on a per employee basis, research and development costs in the pharmaceutical industry are between 2-7 times greater.[16] Extensive testing and clinical trials occur during this phase along with significant regulatory review prior to the approval and introduction of a drug into the market. This period can span years due to the amount of research and regulatory requirements demonstrating efficacy and safety to bring a product to market.

Figure 1 Illustrative Drug Development Lifecycle



The producer of a brand drug enjoys some protection from competition for a time in two ways. One way is from the brand exclusivity period granted by the FDA for new drug applications (NDA) and abbreviated new drug applications (ANDA) meeting specified eligibility requirements by the FDA. These exclusivity periods vary between 6 months and 7 years depending on the type of product or exclusivity (e.g., orphan drug). For new drugs the exclusivity period is 5 years. A second way to obtain market protection is by filing for patent

[16] Darius N. Lakdawalla, Economics of the Pharmaceutical Industry, *Journal of Economic Literature 2018, 56*(*2*), *397–449.*

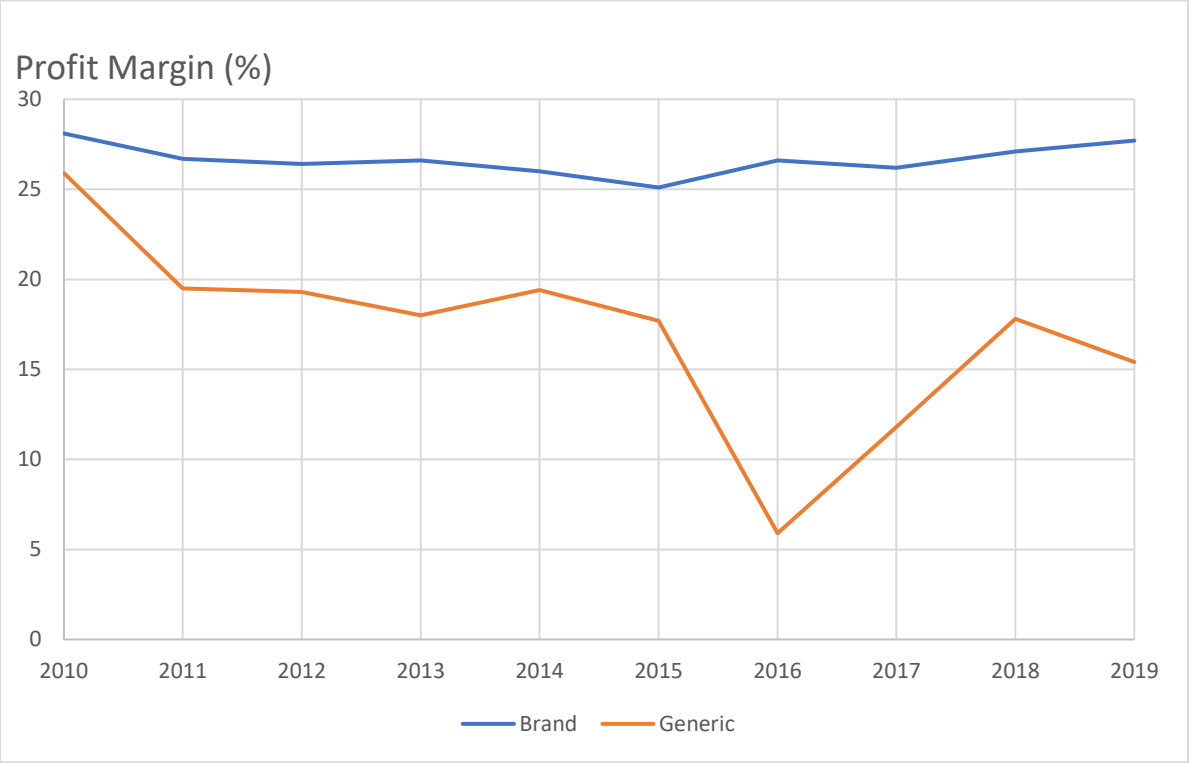
protection which lasts for 20 years. Much of that period runs through the lengthy research, development, and regulatory approval stage such that the average time in which a generic drug is introduced into the market according to one study is about 12 years.[17]

Exclusivity and patent protection affords the developers of a drug a competition-free market for the duration of the exclusivity/patent period whichever is in force at the time. During this period, for companies as illustrated in Figure 1, sales of brand products ramp up as do profits. Drug pricing of brand pharmaceutical products during the exclusivity period permits companies to realize larger and more stable periods of profitability than after the exclusivity period. To gain a sense of the financial performance of the pharmaceutical industry, consider Figure 2 which shows the profitability and revenues for the largest brand and generic companies over time. Brand company profit margin: defined as operating income divided by sales exhibits higher and more stable performance over the same period than generic companies. Once the exclusivity period expires, the product enters the generic phase marked by a near perfectly competitive market for the product. It is during this phase of the lifecycle that this competitive environment tends to greatly lower market share for individual participants and coupled with pricing pressures from policy and demand-side participants, places significant cost containment pressure on the manufacturing of generic products. High research and development costs of brand products coupled with relatively low probabilities of successful transition to marketable products along with eventual generic product competition and patent or exclusivity expiration have in part led to a pattern of industry consolidation and specialization over time that has influenced the pharmaceutical manufacturing process.

While both generic and brand markets do not appear to be as concentrated as other industries such as banking, several mergers and acquisitions among pharmaceutical companies have taken place over the last 10 years. One of the more notable acquisitions recently was the $63 billion acquisition of Allergan by Abbvie. Abbvie, the developer of the popular blockbuster drug Humira derived a disproportionate share of its revenues in recent years from that product and faced patent expiration in 2018. Before it was successful in extending its primary patent to 2034, the acquisition of Allergan positioned Abbvie to diversify its product line.[18]

[17] Kesselheim, Aaron S., Michael S. Sinha, and Jerry Avorn, Determinants of Market Exclusivity for Prescription Drugs in the United States, JAMA Internal Medicine, Special Communication, Health Care Policy and Law, September 11, 2017.
[18] Andrew Dunn, "5 Reasons Why Abbvie Bought Allergan, and Why They May Not Be Enough," Biopharma Dive, June 26, 2019.

Figure 2 Brand and Generic Company Profitability, 2010-2019[19]



Source: Wharton Research Data Services (WRDS), top brand and generic-designated companies.

The high cost of specialized research and development coupled with the advancement of new technologies in immunotherapy and biopharmaceutical development have also transformed industry structure. While a large number of pharmaceutical companies follow a vertically integrated organizational structure entailing all major facets of development, marketing and production, a number of specialty firms have grown in the industry focusing on specific aspects of the pharmaceutical lifecycle including CROs as well as CMOs.[20] Rather than spread costs across all disparate facets of the product lifecycle, contracting out for specialized tasks such as R&D and manufacturing can reduce operating costs for traditional pharmaceutical companies. CMOs with sufficient scale and expertise and access to a global supply chain can provide a potentially lower cost solution for pharma companies under some operating structures than maintaining an internal manufacturing presence.

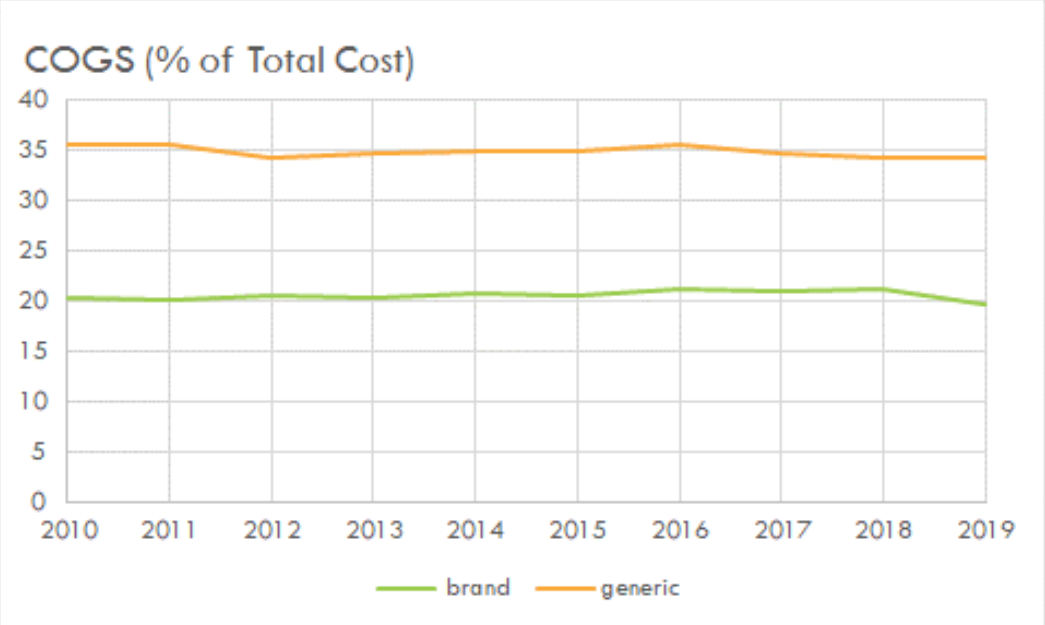
With larger and more stable profit margins, one could argue that brand companies may not be as incented to reduce manufacturing costs as generic companies facing greater competitive pressures. However, research by Vernon et al., suggests that reductions in manufacturing costs

[19] The decline in profit margin in 2016 for generic companies is in part driven by the performance of several large generic companies for that year.
[20] Roots Analysis, Research Report, Pharmaceutical Contract Manufacturing Market (2nd Edition), 2018-2028, 2018.

by way of efficiency gains from better technology or other means of production (cost of goods sold, (COGS)) increase R&D investment, leading to new drug discoveries and products.[21] This proposition was tested and supported empirically by the work of Basu et al. investigating pharmaceutical company manufacturing costs.[22] These studies suggest that both brand and generic companies should be incented to focus on investing in manufacturing technologies that lower their average cost of production. Generic companies would have much to gain from such an economies of scale strategy as well, considering competitive pressures on profit margin.

Decomposing pharmaceutical industry cost structure in both the brand and generic segments provides a better understanding of how manufacturing costs factor into strategic investment decisions by these companies. Figure 3 provides a comparison of cost trends over time for these segments. COGS for both segments were stable over the 2010-2019 period, with generic COGS comprising a much higher percentage of total cost (35%) than brand companies (21%), reflecting in part the lower R&D costs associated with generics compared to brand companies. That higher allocation of costs to COGS for generic companies supports the argument that these firms have an economic incentive to leverage cost-saving manufacturing technologies.

Figure 3 Cost of Goods Sold for Brand and Generic Pharmaceutical Companies: 2010-2019



Source: Wharton Research Data Services (WRDS), top brand and generic-designated companies.

[21] Vernon, J.A., Keener, H.W., and Trujillo, A.J., Pharmaceutical Manufacturing Efficiency, Drug Prices, and Public Health: Examining the Casual Links, *Drug Information Journal,* Volume: 41 issue: 2, page(s): 229-239, March 1, 2007.

[22] Basu, Prabir, Joglekar, Girish, Rai, Saket, Suresh, Pradeep, and John Vernon, Analysis of Manufacturing Costs in Pharmaceutical Companies, Journal of Pharmaceutical Innovation, Volume 3: page(s) 30-40, 2008.

Manufacturing Process and Supply Chain Issues

Further insight on pharmaceutical manufacturing costs can be gained by reviewing the current state of manufacturing including production processes and supply chain developments in the industry. Currently, the FDA oversees more than 4 thousand manufacturing facilities engaged in the production of pharmaceutical products for U.S. consumption (Table 2). More than half of

Table 2 FDA Drug Manufacturing Sites, 2019

Manufacturing Sites	Number	%
US	1793	42
India	505	12
EU	858	20
China	379	9
All Other Countries	741	17
	4276	100

Source: FDA, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Report on the State of Pharmaceutical Quality: Fiscal Year 2019.

these facilities operate abroad. Pharmaceutical manufacturing takes place for both finished dosage form (FDF) and APIs. Most of these facilities operate using a batch processing approach which has been an industry standard technology for decades.

Batch processing typically features a sequential set of production steps. From an engineering perspective, the stages of batch production of OSD products start with acquisition of raw materials which consist of both APIs and excipients, the latter of which are ingredients necessary to the delivery of a pharmaceutical product to a patient but by themselves are not considered an active component to the process. Thereafter, a batch process generally follows the following steps common to any process whether batch or other; blending; wet granulation, drying, milling, blending; compression and coating. A batch process features the potential for more production discontinuity as the process stops at the end of each production step before moving along to the next stage. This can cause delays in the overall production process and more downtimes, making it difficult to optimize efficient plant operation. The vast majority of OSD pharmaceutical products are manufactured via some variation of the traditional batch process.

A major distinction between batch and CM processing is that the latter entails uninterrupted processing of inputs and material through the various stages of production. This approach has several advantages over batch; reductions in manual touchpoints which can improve efficiency in operations and safety to employees; the ability to shrink processing time compared to batch; lower upfront capital investment costs due to smaller facility equipment and land requirements; and greater flexibility to adjust batch size as needed. Two other potentially significant advantages include enhanced product quality and potential for lower environmental liability. A

CM process has the potential to deliver better quality product with lower variability due to enhanced automation and integration of monitoring tools more seamlessly than under batch processes that rely on a more disjointed manufacturing approach.

CM serves as the representative advanced technology for this study due in part to increasing visibility in the industry including participation of a number of companies launching CM facilities under the FDA's ETP and its applicability to a large segment of the drug product set; namely OSDs. Another reason for focusing on CM was the availability of detailed cost analysis of batch and CM facilities for OSD products.

Despite the apparent advantages of CM over batch, the technology has not supplanted batch processing as a viable alternative for pharmaceutical manufacturing. Nevertheless, several of the largest pharmaceutical companies that under ETP have developed and/or applied to build CM projects are listed below:

- Vertex
- Eli Lilly and Company
- Johnson and Johnson
- Merck & Co.
- Pfizer Inc.
- GlaxoSmithKline
- Amgen
- Novartis
- Boehringer Ingelheim

While this interest in CM manufacturing is encouraging, questions remain as to why CM has not garnered more interest as a substitute for batch processing facilities, either for finished products or APIs. There are several possible explanations for this lack of widespread adoption of CM. A common denominator of all of them is uncertainty compared to existing processes. Building a new or retrofit facility using batch manufacturing carries greater certainty of investment and ongoing costs, regulatory requirements, operations, and integration with supply chains given this technology's lengthy industry track record. Although CM technology has been in place for decades in other industries such commodity chemicals and food processing, there has been limited experience with it in the pharmaceutical industry. Reducing financial, supply chain and regulatory uncertainties is essential for CM to replace existing technology more broadly. The stochastic simulation analysis of CM versus batch manufacturing investment presented later in this study provides a basis for exploring these issues in more detail.

Risks and Costs Associated with Pharmaceutical Manufacturing

Pharmaceutical manufacturers face a myriad of risks and costs when producing their products and these considerations factor into what types of manufacturing investments to make, when to make them and where. Cataloging these risk factors is useful in assessing the degree to which investments in advanced manufacturing technology such as CM can be made and how they may

support broadening domestic production of pharmaceutical products. Key risk factors affecting manufacturing investment decisions include the following:

- Reputation Risk
- Regulatory and Compliance Risk
- Geopolitical/External Risks
- Environmental Risk
- Financial Risk
    - Pricing
    - Costs of production
    - Taxes
    - Foreign Exchange
- Strategic/Business Risk
- Operational/Supply Chain Risk
- Legal Risk

While one type of risk may initially manifest, often it can lead to a cascading effect that is a catalyst for another risk to appear. An integrated approach to managing these risks can ensure companies consider not just the unique aspects of each risk type but the complexity of interactions among risks.

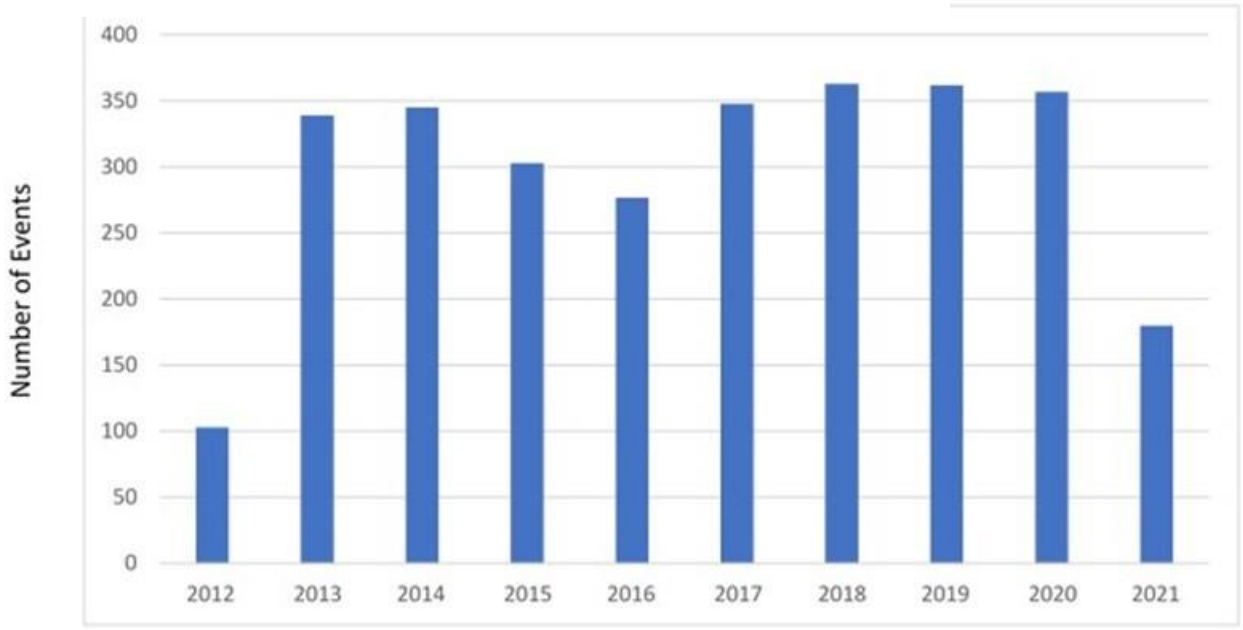
Reputation Risk

Pharmaceutical companies face significant reputation risks given the nature of their products. Drug safety and ensuring a reliable supply of product are two paramount concerns for the industry and FDA alike. The 2008 global recall of the anti-coagulant drug Heparin due to a contaminant traced back to a chemical plant in China received significant media attention at the time. Likewise, the 2018 Valsartan drug recall reverberated through the pharmaceutical and healthcare industries as impurities found in various locations forced healthcare providers to quickly substitute alternative drugs for their patients. Both events precipitated a number of class action lawsuits brought against manufacturers of these products, underscoring the need for assessing pharmaceutical risks on an integrated basis. Drug recalls continue to be a nagging issue for the industry as seen in Figure 4. Product quality is key to mitigating both reputation and regulatory and compliance risk for companies.

Regulatory and Compliance Risk

The pharmaceutical industry is one of the most regulated sectors of the U.S. economy with the FDA overseeing the effectiveness, safety and quality of pharmaceutical products provided to U.S. consumers. The potential for delays in bringing a product to market considering uncertainty over the timing of regulatory approvals for a new technology such as CM presents regulatory and financial risks for pharmaceutical manufacturers compared to well-established technologies such

Figure 4 Drug Recall Trends



Source: FDA Data Dashboard, 2021. Drugs include all product types.

as batch processing. Bringing a pharmaceutical product to market requires a number of ongoing regulatory touchpoints throughout the product lifecycle. One of the most important requirements affecting pharmaceutical manufacturing relates to CGMP. CGMP dictates "minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product."[23] Manufacturers are expected to build effective controls into their process at the outset rather than rely on inspections and testing to uncover manufacturing defects. Particular attention to risk- and quality-based methods has been made by FDA to the industry in the form of ICH Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality Systems). Before a company can be approved for a new or generic marketing application, FDA will review the company's adherence to CGMP. FDA has a number of enforcement mechanisms at its disposal including issuance of warning letters, seizure of "adulterated and/or misbranded" products, injunctions and criminal prosecution and fines. FDA relies on a combination of facility site inspections and company self-identification of issues as key mechanisms for monitoring CGMP compliance. Risk factors considered in FDA's Center for Drug Evaluation and Research (CDER) Site Selection Model (SSM) for a facility include:[24]

- Compliance history;

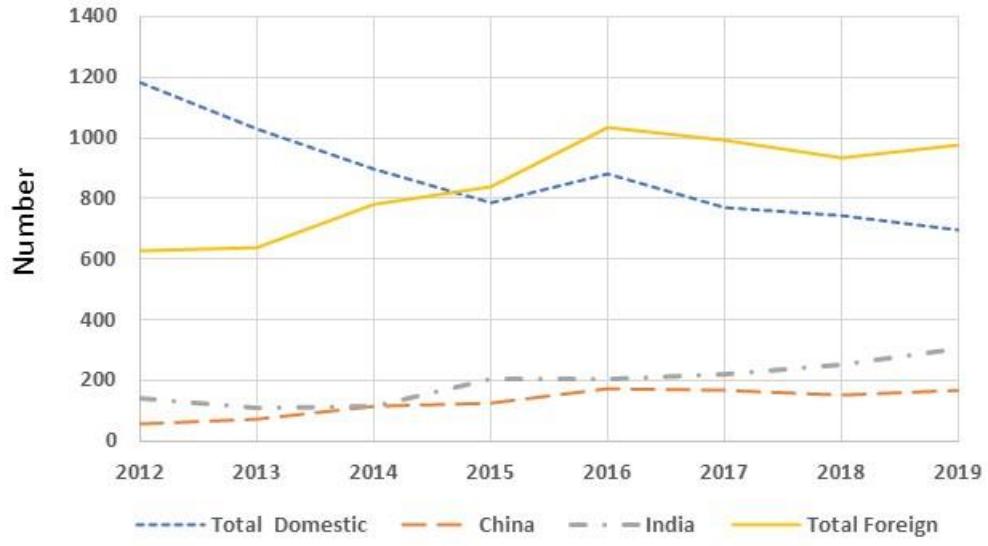
[23] FDA, Current Good Manufacturing Practice (CGMP) Regulations, 2021. Found at https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations.

[24] FDA, Office of Pharmaceutical Quality, Manual of Policies and Procedures, Understanding CDER's Risk-Based Site Selection Model, September 26, 2018.

- History of drug recalls;
- Inherent risk of the drug product manufactured by the facility;
- Inspection frequency and history;
- Facility inspection by a foreign government;
- Other considerations not otherwise described above

The number of inspections over time conducted by FDA in the U.S. and abroad are shown in Figure 5. While most inspections (67.1%) are conducted on U.S. facilities, over time (and before the Covid-19 pandemic) there has been a significant increase in the rate of inspections in countries such as China and India.

Figure 5 FDA Pharmaceutical Manufacturing Facility Inspections



Source: U.S. Government Accountability Office, Testimony before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, Committee on Appropriations, House of Representatives, Statement of Mary Denigan-Macauley, Director, Health Care, Drug Safety - FDA's Future Inspection Plans Need to Address Issues Presented by COVID-19 Backlog, 2020.

Based on FDA inspection data, countries with some of the lowest inspection scores reflecting compliance issues with CGMP include China and India, major producers of APIs and finished dosage products for the U.S. The average inspection score for FY2019 was 7.4. Scores for the EU and U.S. in that year were 7.7 and 7.6, respectively.[25] By contrast scores for China and India were 7.0 and 6.8, respectively. The inspection score ranges between 1-10 and represents a facility's compliance with CGMP practices over the last ten years with more recent inspections carrying greater weight in the scoring system. According to the FDA, all reported scores

[25] Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Report on the State of Pharmaceutical Quality: Fiscal Year 2019.

"indicate an acceptable level of compliance to CGMPs on average." Among the reasons for a citation issued following an inspection, nearly a third were due to some control deficiency such as laboratory controls (19.3%) or process and controls (12.4%).[26] While estimating the total regulatory cost associated with pharma manufacturing remains relatively unknown at the industry level, important components include direct costs of noncompliance in the form of fines, penalties and other sanctions, costs associated with maintaining CGMP standards as well as indirect costs associated with regulatory delays that extend the timing to get products to market.

The use of advanced manufacturing technologies could help reduce regulatory risk for pharmaceutical companies. Under a standard batch manufacturing process, testing is performed following each step. This extends overall processing time and can create undesirable characteristics of the intermediate substance such as powder segregation that could affect the quality of the resulting product. Conversely, a CM process is more automated and thus less susceptible to these potential batch processing issues. There are, however, regulatory issues associated with CM processes. Pharmaceutical products already in place using batch manufacturing processes would require a new submission by the company if they were to replace the batch process with a new process such as CM. While regulatory uncertainties may be a factor that reduces interest in developing CM capabilities, the FDA has signaled their strong interest and support to industry in adopting advanced manufacturing technologies.[27]

Geopolitical/External Risks

The modern pharmaceutical supply chain is a reflection of the ongoing globalization of markets in general that has affected all types of manufacturing in the last several decades. The benefits of globalization include diversification of the pharmaceutical supply chain, which mitigates the potential for disruption of key drug inputs and/or products, lower costs by taking advantage of differential labor, land and other expenses across countries in the manufacturing process, and optimization of supply chain networks in manufacturing and distributing products worldwide for maintaining production continuity.

Nonetheless, this strategic development also exposes companies to external risks. At the outset of the COVID-19 pandemic, for example, concerns rose over the potential for long-term disruptions of the pharmaceutical supply chain as manufacturing sites and transportation activities were temporarily shut down in response. For example, it is reported that early on during the pandemic, India stopped exports on 26 drug products and 13 APIs in an effort to ensure a sufficient supply of drugs for their country.[28] Disruptions in the flow of pharma products to the U.S. due to pandemics or other external events, including climatological events,

[26] FDA, Report on the State of Pharmaceutical Quality: Fiscal Year 2019.

[27] FDA, Emerging Technology Program, October 10, 2019. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program, FDA, Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization, Guidance for Industry, September 2017, and https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program.

[28] Johns Hopkins Bloomberg School of Public Health, The Pandemic and the Supply Chain, Addressing Gaps in Pharmaceutical Production and Distribution, November 2020.

underscore the need for greater attention to hardening the U.S. pharmaceutical pharma supply chain and domestic manufacturing of drug products. This also includes the potential for cyber attacks against pharmaceutical manufacturing sites similar to the one that shut down the Colonial Pipeline in the U.S. in Spring 2021 that severely disrupted access to and pricing of petroleum products for consumers and businesses for a period of time. Greater system automation of CM processes brings certain cost and efficiency benefits discussed earlier but also the potential for cyberbiosecurity threats. Nevertheless, such risks should not be a deterrent to investing in advanced manufacturing technologies but a recognition that these new production methods with their more sophisticated computer-based systems offer an opportunity for companies to augment these technologies with state-of-the-art cyber threat detection capabilities to improve current cyber risk management activities.

Environmental Risk

Pharmaceutical manufacturing, not unlike that of other industries, has the potential to impose measurable negative environmental impacts notably on waterways, and drinking water via wastewater effluent. Air pollution is another potential environmental hazard from pharmaceutical production and both water and air-borne pollutants can harm human and animal life. One of the more concerning aspects from such risks is anti-microbial resistance in humans due to an increase in pharmaceutical by-products reaching water systems.[29] Compounding the problem is differential environmental regulation around the world. In countries such as China and India, environmental laws and regulations have historically tended to be less restrictive than in the EU or the U.S. A number of reports and studies have chronicled environmental crises at locations abroad over the years such as Hyderabad India where excessive levels of pharmaceuticals were found.[30] To the degree that companies considering pharmaceutical plant location in the U.S. versus other countries take the cost of compliance with environmental regulations into account, countries with less environmentally-friendly policies may have a competitive advantage over nations with more stringent environmental regulations. A counter argument could be made, however, that the potential for an environmental disaster to make international headlines might deter companies from purely selecting a site based on environmental costs, particularly in light of greater awareness and attention to environmental, social and governance (ESG) investing in recent years. The use of advanced manufacturing technology such as CM could potentially reduce environmental risks for pharma manufacturers by reducing the amount of waste that could otherwise make its way into the environment.[31]

[29] UN Environment (2017). Frontiers 2017: Emerging Issues of Environmental Concern. Available at: https://www.unenvironment.org/ resources/frontiers-2017-emerging-issuesenvironmental-concern

[30] Larsson (2014). Pollution from Drug Manufacturing: Review and Perspectives. Philosophical Transactions of the Royal Society B: Biological Sciences, 369(1656). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213584/.

[31] Yuji Inada, Mitsui & Co., Continuous Manufacturing Development in Pharmaceutical and Fine Chemicals Industries, Global Strategic Studies Institute Monthly Report December 2019.

Financial Risk

Pharmaceutical manufacturers face a variety of financial risks. Financial risk in this context is defined as the shortfall in cash flow that arises from factors that affect firm profitability.[32] Net cash flow is defined as the dollar amount of cash inflows less cash outflows over some time period such as a year. Cash inflows are defined as all sources of revenues such as from pharmaceutical sales while cash outflows could include costs of goods sold, taxes, costs of hedging foreign exchange for a global pharma manufacturer and general and administrative costs. Net cash flow is more formally defined below as:[33]

$$Operating\ Income = Revenue - COGS - G\&A - D - T - R\&D - HC$$

Where COGS represents the cost of goods sold; G&A is general and administrative expenses; D is depreciation; T is taxes; R&D is research and development costs, and HC is foreign exchange hedging cost.

Companies deciding whether a project is financially viable often rely on NPV analysis or its variants.[34] Traditionally, NPV analyses are performed in a deterministic manner, i.e., without any degree of uncertainty introduced. A later section of the study will introduce a stochastic simulation approach to the NPV analysis taking into account uncertainty in specific components of manufacturing cash flows. This approach allows for a distribution of potential NPV outcomes to be analyzed.

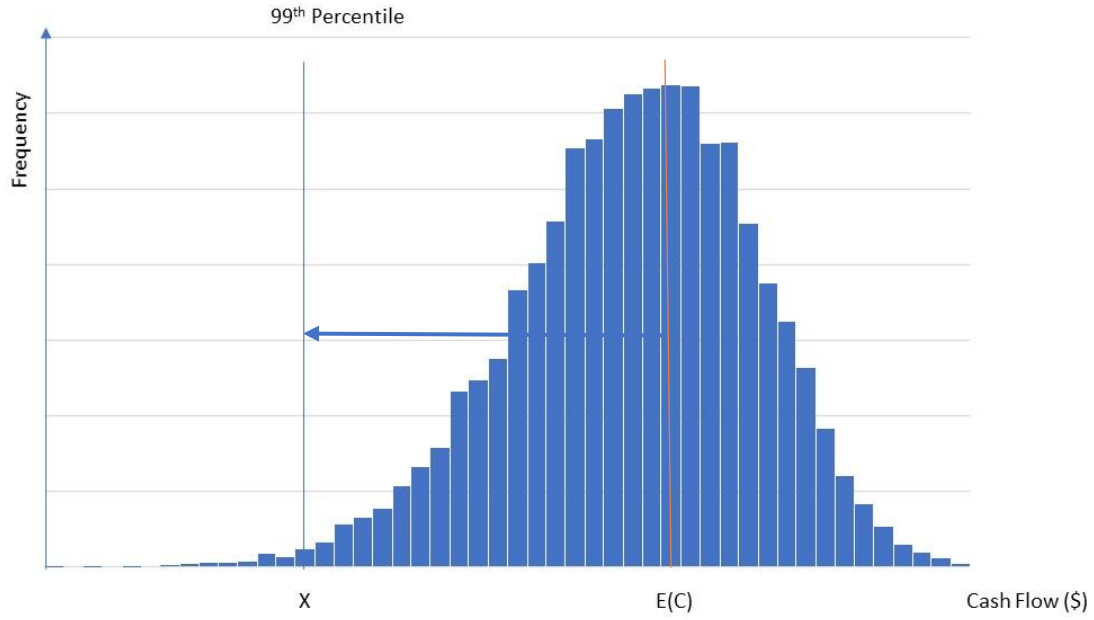
In the case of a firm's financial risk, a company is concerned about having sufficient cash inflows to satisfactorily cover cash outflows over some time with a certain degree of confidence. If at some point, a company faced distress such as bankruptcy due to insufficient cash inflows, it could go out of business or be forced to merge with another company. To illustrate this concept, assume that a company has determined that there is a 1 percent chance that a cash flow shortfall of X dollars below its expected cash flow would put the firm into financial jeopardy. X represents the dollar amount of cash flow at-risk (CaR) with probability p of 1 percent. A company could frame its financial risk then as wanting to manage its business in a manner to be 99 percent confident of not experiencing a financial distress event. This can be depicted in Figure 6. The histogram represents a discrete distribution of operating income outcomes for a company over a year. On average, this company could expect to see operating income of an amount E(C) which in a normal year would be some positive amount. Depending upon market conditions and other factors, a wide variation in operating income could occur over a year. Drivers of such variability could include changes in the amount of sales and/or unit pricing due to changes in product competition, or variability in various cost components of operating income. The firm in this example would want to manage its business in a manner to ensure its

[32] Rene M. Stulz, Risk Management & Derivatives, Thomson South-Western, 2003, p. 89.
[33] Prabir Basu, Girish Joglekar, Saket Rai, Pradeep Suresh, and John Vernon, "Analysis of Manufacturing Costs in Pharmaceutical Companies, Journal of Pharmaceutical Innovation, (2008), 3:30-40.
[34] Real options analysis has become an alternative to standard NPV analysis in recent years.

operating income does not fall below the level of X in Figure 6. It could for example, raise equity as a buffer to mitigate the negative consequences from breaching its CAR.

Variability of operating income thus gives rise to financial risk. The nature of the product lifecycle as discussed earlier in the pharma industry contributes to cash flow variability in a number of ways. Product pricing and sales fall precipitously once the product moves from having brand protection to generic status. A study by Conrad and Lutter, for example, found a significant difference in the ratio of prices for generic and brand drugs and those differences became more pronounced as the number of generic competitors entered the market.[35] When one generic producer existed for a drug, the ratio of median generic average manufacturers price (AMP) to brand equivalent price was .614 vs .144, for example, for 5 generic producers in a market and .010 for 10 or more producers.

Figure 6 Cash Flow-at-Risk Concept



Other sources of financial risk for pharma companies include cost variability. For brand companies, initial investments in R&D are considerable. Lakdawalla, notes that investments in a new biopharmaceutical product can approach $2.5 billion.[36] Such upfront expenditures tend to be driven in the pharma industry more by firm cash flow due to hypothesized capital market

[35] Ryan Conrad and Randall Lutter, FDA, Center for Drug Evaluation and Research, Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices, December 2019.
[36] Darius N. Lakdawalla, Economics of the Pharmaceutical Industry, *Journal of Economic Literature 2018, 56*(*2*), *397–449.u*

imperfections in the industry. Variations in R&D investments have been hypothesized and supported empirically to suggest that pharma companies will leverage lower cost internal funds available from their profits before turning to external sources.[37]

Manufacturing cost uncertainty presents another source of financial risk to pharma manufacturers. As noted in Figure 3, COGS account for approximately 35% and 20% of generic and brand manufacturing expenses, respectively.[38] From the standpoint of investing in advanced manufacturing technology, companies need to consider variations in upfront and ongoing costs associated with new processes that do not have established track records in the industry. This cost uncertainty could lessen interest in advanced technologies such as CM over standard batch technology that has more extensive application in the industry and therefore greater cost reliability for estimating project feasibility.

Other factors affecting firm financial risk include taxes and foreign exchange exposure. Differential tax rates between countries affect firm after-tax profitability and hence create economic incentives for capital flows across the globe. Global corporate tax systems are highly complex and understanding the full impact of a company's tax liability requires an integrated assessment of all components of a company's potential tax burden. In addition to varying corporate tax structures, the form of corporate taxation in a country can affect overall tax burdens that in turn influence investment decisions including facility location. These include value-added taxes (VAT), beneficial taxation on intellectual property (Global Intangible Low-Taxed Income (GILTI)) and other tax credits and subsidies. Changes in tax policy in the U.S. or abroad could affect the location of a manufacturing site and possibly the type of technology applied if tax incentives were in place to encourage processes such as CM that addressed some apparent market failure. In this case, an argument could be made that pharmaceutical safety and uninterrupted access is a public good that the private market cannot assure. Consequently, tax credits or other incentives might be a mechanism by which the government could encourage greater use of advanced technology in pharmaceutical manufacturing in the U.S.

For global manufacturers, fluctuations in foreign exchange rates pose a financial risk to the firm. To illustrate this risk, assume a generic pharmaceutical manufacturer with a manufacturing facility in Ireland generates €1 billion in revenue from that site each year for sale in the US. Assume the $/€ exchange rate is $1.22/€ currently. In U.S. dollars, revenue would total $1.22 billion. Suppose a week later the $/€ exchange rate fell to $1.10/€. Revenue would fall in dollar terms to $1.1 billion, or a loss due solely to foreign exchange risk of $120 million. Typically, such firms do not have an appetite for currency exchange risk and therefore tend to hedge it using a variety of financial derivative instruments. Let's further suppose that the company wants to ensure that over the next 60 days its exposure to currency risk is minimized. In the above example, the company could take an offsetting position in a $/€ futures contract for an optimal number of contracts that over a 60-day horizon would result in a gain to the position of $120

[37] Vernon, John A. 2005. "Examining the Link between Price Regulation and Pharmaceutical R&D Investment." *Health Economics* 14 (1): 1–16.

[38] In addition to COGs, total expenses would include R&D, sales, and general and administrative.

million in the event of a depreciation of the Euro to the U.S. dollar. Such programs, while effective at mitigating this risk impose other costs. Hedge trading groups can be established internally or outsourced to another company at a cost. Moreover, a variety of transaction and related costs are associated with such activities. Leveraging advanced manufacturing technologies that incent domestic manufacturing of pharmaceutical products would have a side benefit of reducing or eliminating hedge costs associated with U.S. global manufacturers' currency risk exposure.

Strategic and Business Risks

A major risk to any company is strategic risk which reflects potential losses associated with poor business and/or strategic decisions for a company. Looking at other industries such as banking during the years leading up to the 2008 Global Financial Crisis, poor decisions relating to mortgage loan manufacturing quality, origination of riskier loan products and fast growth models with weak processes and controls to support that business led to a number of spectacular bank failures. The pharmaceutical industry is no less susceptible to strategic risk. The industry is fraught with a number of existential threats from within and without including continued pricing pressure from large pharmaceutical purchasing organizations and public policy, fierce competition within the generic market and between generic and brand companies, and business disrupting technological changes including increased demand for and development of biopharmaceutical products, the rise of artificial intelligence and big data, and advanced manufacturing technologies. Moreover, the industry has been plagued by overcapacity, ongoing drug shortages and management of vast and complex supply chain networks. These issues were compounded during the pandemic as demand for certain medications rose sharply to address Covid-19 patient needs and manufacturing plants were forced to shut down early on during the crisis due to government-mandated lock-downs. Even after the lock-downs, manufacturing has struggled to reach full capacity due to understaffing as the pandemic wears on.[39] All of these issues have implications for how the pharmaceutical industry can quickly adapt to changing business conditions and external events going forward.

Leveraging advanced technologies to thrive in the highly competitive and regulated pharmaceutical market can provide a competitive advantage to pharma manufacturers in this environment. However, the pharmaceutical industry in some respects is a story of bifurcated technological adoption. Large R&D investments by brand and specialty drug R&D companies over the years have led to a number of technological breakthroughs in drug types, with such spectacular examples as mRNA-based COVID-19 vaccines that revolutionized a wide range of pharmaceutical products available on the market. However, adoption of new technology for pharma manufacturing has been lackluster at best. What explains the apparent dichotomy between pharma R&D and manufacturing technology innovation?

[39] The Johns Hopkins Bloomberg School of Public Health, The Pandemic and the Supply Chain, Addressing Gaps in Pharmaceutical Production and Distribution, November 2020.

Market factors appear to play a large role in shaping management attitudes and strategies toward investing in manufacturing technology. The industry today generally faces issues with overcapacity. U.S. pharmaceutical manufacturers recorded a capacity utilization rate of 71.8 in the 4th quarter 2020 compared to 75.1 for all manufacturers.[40] And the pharma manufacturing index stands much lower than comparable industries such as inorganic chemical and petroleum manufacturing indexes during the same period of 83.2 and 86.3, respectively.[41]

In addition to overcapacity, the industry relies heavily on batch manufacturing processes that can elongate processing times and increase the potential for product quality issues as well. Batch manufacturing is well-entrenched as a standard process used in the production of pharmaceuticals as is the regulatory process associated with the drug approval process. For companies focused on brand pharma products, R&D expenditures account for 15-25% of these companies' total revenues and product innovation has intensified, leading to higher costs with low likelihoods of product realization.[42] Relative to their R&D expenditures, brand companies spend $1.69 on manufacturing costs for every dollar of R&D spending. By contrast, generic companies spend $6.13 in manufacturing costs per dollar of R&D.[43] This is a reflection of the heavier emphasis on R&D spending by brand companies relative to generic firms.

Process manufacturing technological investment has to some degree historically appeared to be a second-order consideration of brand companies relative to front-end product development that is vital to their franchise viability. Outsourcing to companies specializing in manufacturing such as CMOs and offshoring of manufacturing has been a trend in the pharmaceutical industry for many years, in part a reflection of a strategy by a number of companies to optimize their allocation of capital by focusing on strategies to lower their cost structure and maintain competitiveness in the industry. Such strategies can, however, lead to suboptimal outcomes such as delays in product launches and/or missed opportunities to meet product demand.[44]

Management cognitive biases can also play a role in shaping corporate investment attitudes toward technology adoption. For example, in a study of nearly two dozen development projects of pharmaceutical companies, Pisano and Wheelwright found that a leading factor in the failure of these products from realizing their market potential was an inherent bias by management that "process technology was not that important."[45] For generic companies, financial factors may be more likely to determine their likelihood of investing in advanced manufacturing technologies. With a market for generics that is generally much like perfect competition, profit margins as reviewed earlier are much lower and their variability higher than brand companies. With existing batch process excess capacity on hand, significant upfront capital investments in

[40] Capacity utilization rate measures a plant, company, or nation's ability to realize its full manufacturing potential. A percentage less than 100% indicates production falls short of potential capacity.
[41] United States Census Bureau, Quarterly Survey of Plant Capacity Utilization Full Rates: 2020 Quarter 4
[42] Dan Spitzer, IBISWorld, Brand Name Pharmaceutical Manufacturing in the US, August 2020.
[43] Author's calculations from data in Basu et al.
[44] Gary P. Pisano and Steven C. Wheelwright, The New Logic of High-Tech R&D, Harvard Business Review, September-October 1995.
[45] Pisano and Wheelwright.

technologies like CM might hamper a generic company's ability to adopt more advanced manufacturing processes despite the prospect of long-term positive NPV payoffs. This may also be an issue for smaller brand companies with higher cost structures. Compounding this issue are tendencies and reinforcing market activities that can bias managers toward focusing on short-term financial outcomes at the expense of longer-term benefits which could lead to suboptimal strategies and outcomes. Publicly traded companies, for instance, face ongoing pressure to emphasize short-term earnings given investor focus on a recurring basis. This phenomenon can undercut projects that may realize potentially higher NPV over the long run.

Operational Risk

Pharmaceutical manufacturing is subject to considerable operational risk which can lead to reductions in profitability, higher costs and impose other risks on firms. Operational risk is associated with deficiencies in process, people or technology or external events that have adverse financial and nonfinancial consequences for the organization. In the case of pharmaceutical manufacturing, operational risk can manifest in the form of human error or underlying process weaknesses that lead to product contamination, higher scrap rates, greater risk of environmental hazards and employee safety risk, more manufacturing downtimes and longer processing periods than desired. These in turn raise firm costs and/or expose a firm to potential regulatory scrutiny as well which brings its own set of costs. Companies that can objectively compare batch versus CM manufacturing processes taking into account these factors are in a better position to understand how manufacturing quality can lead to improved financial and nonfinancial outcomes.

Supply chain risk

Supply chain risk reflects a company's ability to secure inputs to production or provide its products to market in a timely and cost-effective manner. The COVID-19 pandemic underscored how supply chain disruptions impeded the ability of manufacturers to get their products to market, costing businesses billions of dollars of lost revenue and/or higher costs of obtaining inputs for manufacturing their products. These risks impose downstream effects on consumers in the form of potentially higher prices and/or lack of access to a product. During the pandemic, the distribution of mRNA-based COVID vaccines became a logistical challenge due in part to the extreme low temperature storage requirements for those vaccines. The potential for supply chain risk manifests in several ways; transportation and logistics; planning and supplier networks; financial resiliency, product complexity and organizational maturity.[46] The pharmaceutical industry faces a high level of inherent supply chain risk in large measure due to extensive and complex global supply chain networks operating in a highly regulated industry focused on consumer safety. While unexpected and unintentional disruptions to the

[46] Knut Alicke, Ed Barriball, Susan Lund, and Daniel Swan, McKinsey and Company, Is Your Supply Chain Risk Blind – Or Risk Resilient? May 14, 2020.

pharmaceutical supply chain can impose serious risks to the safety and welfare of U.S. consumers and patients, the threat of intentional disruptions brought about by adversarial nation-states or other actors presents another dimension to this risk.

In testimony to Congress, a high-ranking FDA official outlined the case for why pharmaceutical supply chains present a national security issue for the U.S.[47] Factors cited in this testimony as affecting the degree of drug supply chain vulnerability to national security threats were: dependence on other countries for APIs, U.S. manufacturing resiliency to produce APIs and U.S. manufacturing reliability. The fact that the FDA does not have sufficient data to fully understand the impact of these factors on the supply chain is a sobering reality and one that has jump started government leaders into a call for action. A number of bills in Congress have been proposed to induce more domestic manufacturing of pharmaceuticals in the U.S. and the Biden Administration issued an executive order in February 2021advocating and supporting development of more resilient and secure supply chains in critical industries including pharmaceuticals. While advanced manufacturing technology has a role to play in this strategic objective, it cannot alone drive further investment in domestic pharmaceutical manufacturing in the U.S. The extent to which leveraging advanced manufacturing capabilities can enable more resilient and secure U.S. production of pharmaceuticals depends on developing domestic access to APIs, and reducing regulatory, financial and environmental uncertainty for pharmaceutical manufacturers.

Legal Risk

Companies face legal risks in the form of class action lawsuits and associated awards made to affected parties arising out of court-determined liability on behalf of an entity that through implicit or explicit action or inaction creates some harm to another party. Product liability risk in the pharmaceutical industry has been a major source of legal risk over the years. Legal risks associated on the manufacturing side include legal rulings and awards made relating to environmental hazards or employee/consumer injuries and the like. To the extent that advanced manufacturing processes can reduce the likelihood of such adverse events, they in turn could reduce legal liability as well.

A Financial and Risk Analysis of Continuous Manufacturing

A Theoretical Model of Pharmaceutical Manufacturing Investment

To better understand the economics and risks associated with investing in advanced manufacturing processes by pharmaceutical companies, a multi-period empirical analysis is performed comparing investment strategies in batch versus CM manufacturing. A net present value (NPV) analysis is a standard methodology used in determining whether a potential

[47] Woodcock, Janet, FDA, Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program, Congressional Testimony, October 30, 2019.

investment is economically viable or not. For a project with a projected lifespan of N years, its NPV is calculated as below:

$$NPV = \sum_{n=0}^{N} \frac{(CFI_n - CFO_n)}{(1+r)^n} - I_0$$

where CFI_n and CFO_n represent cash inflows and outflows, respectively, r is the required rate of return or discount rate and I_0 represents the initial investment cost. This static representation of NPV characterizes the investment decision along a single path of cash flows. However, a more realistic view of cash inflows, outflows and investment costs would incorporate some form of variability in cash flows and costs over many possible outcomes.

In the following analysis, we assume pharmaceutical companies are risk-averse and their utility functions follow von Neumann-Morgenstern axioms under uncertainty. Pharmaceutical manufacturers are further assumed to produce brand or generic drugs based on a twice differentiable continuous production function using manufacturing and nonmanufacturing inputs x_M and x_{NM}, respectively. Manufacturing efficiency is in turn a function of technology ($\varphi(\alpha)$) represented by a vector of batch and CM engineering and process-related factors α where $0 < \alpha < 1$. The production function is thus characterized as:

$$q = f(\varphi(\alpha)x_M, x_{NM})$$

The objective of the pharmaceutical manufacturer is to maximize expected utility of profit (ω) ($U(\omega)$), where $U(\omega)$ is the von Neumann-Morgenstern utility function, a standard assumption in economics for production under uncertainty. This approach is comparable to Lakdawalla's characterization of the optimal investment in pharmaceutical research and development.[48] In the theoretical model of a pharmaceutical manufacturer, uncertainty is introduced in the form of three stochastic variables; pharmaceutical sales (production), CM technology operating costs and initial investment costs of CM technology. The generalized form of the pharmaceutical manufacturer's objective function is the following:

$$Max\ E\{U(\omega)\} = Max \int \Big\{\Big(U\big(pf(\varepsilon_P, \varphi(\alpha)x_M, x_{NM})d\theta_P - g(\varepsilon_M, r_M x_M \Delta_i)d\theta_M(\varepsilon_M) - r_{NM}x_{NM} - hc\big) - j(\varepsilon_I, I\Delta_i)d\theta_I(\varepsilon_I)\Big)\Big)(1 - MTR_i)\Big\}(\varepsilon_P)$$

where

- p = OSD price per unit
- ε_P = a random variable for production risk associated with the OSD manufacturing process with distribution Θ_P

[48] Lakdawalla (2018).

- ε_M and ε_I = random variables for manufacturing costs and capital investment, with distributions Θ_M and Θ_I, respectively
- r_M and r_{NM} represent input costs for manufacturing and nonmanufacturing inputs, respectively
- Δ_i = country i manufacturing cost competitiveness factor
- hc = foreign exchange hedging costs
- MTR_i = marginal corporate tax rate of country i
- I = capital investment cost at time 0

A pharmaceutical manufacturer is further assumed to decide whether to invest in CM technology in the United States or use batch technology in either the U.S. or abroad. CM technology is assumed to be more efficient and thus increase pharmaceutical manufacturing productivity such that $\varphi(\alpha_{CM}) > \varphi(\alpha_{Batch})$. The parameterization of these productivity factors leverages a cost study of CM versus batch processing for a new OSD facility described in more detail below. According to this construct, a pharmaceutical company will adopt the advanced CM manufacturing technology whenever the following holds:

$$E\{U(\omega_{CM})\} - E\{U(\omega_{Batch})\} > 0$$

For the CM and batch technology scenarios, this can be represented in terms of a firm's objective function as:

$$Max \int \left\{\left(U\left(pf\left(\varepsilon_P, \varphi(\omega^{CM})x_M^{CM}, x_{NM}\right)d\theta_P(\varepsilon_P) - g(\varepsilon_M, r_M^{CM}x_M^{CM}\Delta_i)d\theta_M(\varepsilon_M) - r_{NM}x_{NM} - hc\right) - j(\varepsilon_I, I^{CM}\Delta_i)d\theta_I(\varepsilon_I)\right)\right)(1 - MTR_i)\right\}(\varepsilon_P)$$

$$Max \int \left\{\left(U\left(pf\left(\varepsilon_P, \varphi(\omega^{Batch})x_M^{Batch}, x_{NM}\right)d\theta_P(\varepsilon_P) - g\left(\varepsilon_M, r_M^{Batch}x_M^{Batch}\Delta_i\right)d\theta_M(\varepsilon_M) - r_{NM}x_{NM} - hc\right) - j(\varepsilon_I, I^{Batch}\Delta_i)d\theta_I(\varepsilon_I)\right)\right)(1 - MTR_i)\right\}(\varepsilon_P)$$

Model Parametrization and Assumptions

Implementation of the theoretical model requires specific information of the costs and approximate relative efficiencies of batch and CM pharmaceutical manufacturing technology. As a result, the empirical analysis is dependent on the availability and reliability of such information. The analysis is confined to manufacturing of OSD products using CM or batch technology based on an important study of CM and batch costs by Schaber et al.[49]

[49] Schaber, SD, Gerogiorgis, DI, Ramachandran, R, Evans, JMB, Barton, PI & Trout, BL 2011, 'Economic

Schaber et al. undertook a study to compare the discounted costs associated with CM versus batch technology for a representative OSD product. The analysis focused on comparing costs between CM and batch processes for a "high-volume" production scale of 2,000 tons of tablets per year. The study provided engineering-based estimates of various inputs of production such as raw materials along with detailed operating and capital cost estimates. The results from the Schaber et al. study are used for this analysis. The inputs of interest include the estimated operating and capital costs associated with batch production along with the study's estimates of cost factors associated with CM technology. Specifically, the Schaber et al. estimates of $226M and $346M for a new facility's batch processing operating and capital costs, respectively are used.[50] Moreover, for CM operating and capital costs, the cost factors from the Schaber et al. study are used for those components associated with their CM process that uses a single recycling loop which provides a higher quality CM process according to the study's authors.[51] Operating costs in the study considered labor, material handling, utilities, waste disposal as well as QA/QC expenses. A 10% premium on CM equipment was imposed by Schaber et al. to account for additional process engineering expense. Applying the Schaber et al. CM operating and capital cost efficiency factors of -20% and -33% which they derived from detailed cost analysis of batch and CM processes, respectively to the batch process dollar cost estimates above translated into CM operating and capital costs of approximately $181M and $232M, respectively.

The Schaber et al. study is noteworthy for its findings that CM processes generated discounted costs that were 9 to 40% lower than batch processing depending on the API mass loading, key ingredient cost and CM technology scenario used. In the case of the CM with recycling scenario assuming the $500/kg key ingredient cost and 10% API mass loading scenario, discounted costs of CM were 22% lower than batch. Despite the analytic rigor associated with the Schaber et al. study, the results have come under some scrutiny. Manning and Sciacca, for example, contend that study relied more on expert judgement in developing estimates rather than on empirical observations.[52] With a paucity of publicly available data on CM costs, the expert judgment approach taken by Schaber et al. is entirely consistent with discounted cost analysis conducted extensively by organizations for a wide range of engineering-intensive investment projects. To be sure, the study does have other limitations that may reduce the significance of the findings. Two of the most significant limitations are that the study focuses only on costs and presents the model in a deterministic framework. By focusing only on manufacturing costs, the Schaber et al. study ignores the impact of cash inflows on the investment decision. As discussed earlier, this

Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study' Industrial and Engineering Chemistry Research, vol 50, no. 17, pp. 10083-10092., 10.1021/ie2006752

[50] These estimates assume an API mass loading of 10% and accost of key ingredients of $500/kg which was the middle of the Schaber et al. cost estimates for key ingredients.

[51] As described by Schaber et al., the CM with single loop recycling increases the effective yield from the first step of the CM process by introducing a step for separating and recycling materials.

[52] Manning, Richard and Rich Sciacca, Bates White Economic Consulting, Continuous Manufacturing in Pharmaceuticals: Economic and Policy Issues, October 2018.

can be a significant factor in whether a company chooses to invest in CM or not. Pricing and competition in brand and generic markets could make the difference between the type of firms likely to adopt CM technology over batch manufacturing processes. Further, any such study of advanced manufacturing should take into account the distribution of potential cash flows in producing pharmaceuticals. Nor does the Schaber et al. study address U.S. versus nonU.S investment decisions. As a result, this study offers the first stochastic NPV simulation comparing CM to batch technology for pharmaceutical manufacturing. The study focuses only on new construction and not plant retrofit as a scenario. It also assumes the same large scale of production assumed in the Schaber et al. study. With additional data and information on CM costs for smaller scale production and retrofit costs, this model could easily be extended in the future to handle those scenarios.

The definition used for NPV in the model is as follows:

$$NPV = \sum_{t=1}^{T} \frac{(Revenue_t - MOpEx_t^{\alpha}\Delta - NMOpEx_t \ - hc)(1 - MTR_i)}{(1+r)^t} - MCapEx_0^{\alpha}\Delta$$

where

- Revenue represents annual sales of the pharmaceutical OSD product;
- MOpEx is manufacturing operating expense for technology α (i.e., batch or CM);
- NMOpex is nonmanufacturing annual costs;
- hc represents foreign exchange hedging costs;
- MTR is the marginal corporate tax rate for country i;
- MCapEx is the capital cost associated with technology α; and
- r is the discount rate

Two additional assumptions in the analysis included the project time horizon and brand loss of exclusivity period. The Schaber et al. study assumed a 15-year project horizon, however, this is likely to be much smaller than the actual lifecycle for a new drug.[53] For this analysis, a 20-year horizon was applied. The analysis also assumed that LOE occurred after the 12th year of the analysis. This estimate is based on a number of studies cited by Kesselheim et al. that estimated LOE periods for various drug products over time.[54]

In order to align the Schaber et al. study cost estimates for batch and CM manufacturing processes with actual pharmaceutical industry financial structure information, revenues and nonmanufacturing costs were scaled to be consistent with the WRDS data for brand and generic company historical profit margin. To derive these components of NPV for the model, total operating cost (TOC) for brand and generic companies was computed based on the average of

[53] Lakdawalla (2018).

[54] Aaron S. Kesselheim, Michael S. Sinha, Jerry Avorn, Determinants of Market Exclusivity for Prescription Drugs in the United States, JAMA Internal Medicine, AMA Intern Med. doi:10.1001/jamainternmed.2017.4329 Published online September 11, 2017.

historical cost of goods sold (COGS) as a percent of TOC. The calculation for TOC for company type k (brand or generic) and manufacturing type α (CM or batch) used is as follows:

$$TOC_{\alpha}^{k} = \frac{MOpEx_{\alpha}}{COGS\%^{k}}$$

Revenue for the model was derived as follows:

$$Revenue_{\alpha}^{k} = \frac{TOC_{\alpha}^{k}}{PM^{k}}$$

In this formula, PM represents the historical profit margin (in percent) for company k. NPV revenue, cost and discount rate inputs used in the analysis are shown in Table 3. Discount rates were generated from WRDS historical data.

Table 3 Model NPV Inputs

NPV Component	Brand Company	Generic Company
Revenue ($M)	$1,569	$813
MOpEx ($M)		
CM	$181	$181
Batch	$226	$226
NMOpEx ($M)	$910	$439
MCapEx ($M)		
CM	$232	$232
Batch	$346	$346
Discount Rate (%)	6.76	6.14

The three stochastic variables in the model; Revenue, MOpEx and MCapEx were assumed to follow a generalized Weiner process with a constant drift rate and variance. The discrete form of each stochastic variable is represented by the following:

$$\frac{\Delta V}{V} = \mu\Delta t + \sigma\epsilon\sqrt{\Delta t}$$

$$\Delta V = \mu V\Delta t + \sigma V\epsilon\sqrt{\Delta t}$$

Where μ is the drift rate, σ is the standard deviation (volatility) of variable V and ε is a random normal variable. It is assumed, following convention with other cost studies, that operating, and capital costs are lognormally rather than normally distributed as are revenues.[55] The lognormal distribution ensures nonnegative costs and revenues and also better reflects the tendency that

[55] NASA, Cost Estimating Handbook Version 4.0, Appendix G Cost Risk and Uncertainty Methodologies, February 2015.

costs are more likely to go up than down. It can be shown that if a random variable y is a function of x or y = y(x), then the probability density function of y and x is the following:

$$f(y) = f(x)\frac{dx}{dy}$$

And if x follows a normal distribution, then $y = e^X$ is lognormally distributed. In order to generate lognormal distributions for costs and revenues we need to generate a lognormal random variable. The process used was to generate 10,000 standard normal random variates Z. By letting $x = \mu + \sigma Z$ where μ and σ are parameters of the lognormally distributed random variable over 10,000 simulations we can generate y, a lognormally distributed variable. The simulation process thus entailed generating separate lognormal distributions of revenues and costs for the different technology outcomes. To align the U.S. and nonU.S. technology outcomes, we generated the nonU.S. outcome sales and cost distributions by applying the same random variables used in the U.S. outcome. Then the NPVs were computed for each of the 10,000 trials to generate a distribution for the batch and CM technology outcomes.

For the analysis, μ is set at 0. The long-term drift in revenues and manufacturing costs would affect nominal NPV, but since we are interested ultimately in net NPV between CM and batch technologies, this assumption has no effect on the result of interest; namely the net NPV of CM and batch scenarios. Estimates for revenue volatility, however, are developed from the historical WRDS data. For brand and generic companies, the estimates used in the model for annual revenue volatility were 7.1% and 27.5%, respectively. A baseline annual volatility for manufacturing operating and capital cost was set at 2.5% based on a study by Achilleos et al..[56] Versions of the model were coded and tested using Python and Excel VBA.[57] For each scenario, 10,000 simulated NPVs were generated in order to obtain a reasonably shaped distribution, particularly the left-hand (negative NPV) tail of the distribution. A total of 156 different scenarios were run on combinations of the following attributes:

- Company type (Brand/Generic)
- Manufacturing Type (CM/Batch)
- Country (US/India/Ireland/China)
- CM Cost Volatility (2.5%/10%/15%)
- Profit Margin Volatility
    - Brand 15% (Yrs. 1-12)/10% (Yrs. 13-20)
    - Brand 10% (Yrs. 1-12)/5% (Yrs. 13-20)
    - Brand 5% (Yrs. 1-12)/0% (Yrs. 13-20)
    - Generic (10%/5%/0% Yrs. 1-20)
- US Tax Rate (21%/28%)

[56] Evdokia C. Achilleos, John C. Calandranis, and Demetri P. Petrides, Quantifying the Impact of Uncertain Parameters in the Batch Manufacturing of Active Pharmaceutical Ingredients, PHARMACEUTICAL ENGINEERING® The Official Magazine of ISPE July/August 2006, Vol. 26 No. 4.

[57] A publicly available version of the model is available upon request from the author.

- Foreign Exchange Hedging Cost Variability (1%, 2%, 4%)

Note that for the brand company scenarios, an assumption is made to switch over to generic revenues starting in year 13 reflecting a loss of exclusivity. The specific scenarios for brand and generic companies tested are found in Tables 4 and 5. The 10% and 15% CM cost volatility scenarios as well as the profit margin and foreign exchange hedge cost scenarios were intended for sensitivity analysis of the results to key NPV drivers. Other key model inputs included comparative manufacturing productivity rates for China, India and Ireland and corporate tax rates for these countries. Table 6 provides details on these inputs. All hedge costs scenarios assumed currency risk was fully hedged but the cost associated with buying and selling hedge instruments varied from 0% (baseline) to 4%.

Each of the 156 scenarios compare a baseline (e.g., U.S. CM) to a challenger country/technology alternative (e.g., China/Batch). While the entire distribution of NPVs is generated for the baseline and alternative, this study is most interested in the expected NPV (E(NPV)) as well as two measures of NPV tail risk: the 95th and 99th worst (lowest) NPVs among the 10,000 simulated NPV values for each scenario. In a stochastic NPV simulation, E(NPV) is useful as it provides a more robust estimate of a project's financial prospects than a single deterministic path assessment. However, making a business decision on a costly project should also consider the risk of that project as depicted in the tail of the distribution. In the financial services industry, for example, value-at-risk, or VaR is a way of measuring the risk of a decline in value of a bank's trading book over some period of time (e.g., 1 day). A bank will generate a distribution of the end of trading day portfolio value and compare that value to some board-approved VaR. For example, assume that the risk office of a bank has looked at historical portfolio values and found that the 99th percentile worst daily portfolio trading loss was $1billion and the board sets this as the 1-day VaR for the bank. This would mean that the 99 percentile worst allowable loss over a single day would be $1 billion and the bank would hold additional capital to guard against that loss.

A variation of this VaR concept can be leveraged in the case of pharmaceutical manufacturing investment decisions by comparing the distributions of net NPV for the baseline and country/technology alternative and using a percentile of the lowest net NPV as an investment VaR. This application is similar in construct to cash flow-at-risk presented in Figure 6 and Figure 7 describes the application of project investment VaR in this study.

For a particular scenario, NPV distributions for the country/technology baseline and alternative are generated (Panels A and B). The difference, referred to as net NPV across each of the 10,000 trials for each scenario (e.g., [US CM – U.S. Batch] NPV) is depicted in Panel C. If a company wanted to be 99 percent confident that an investment in CM technology would result in a higher NPV than batch, then they would select X as their target net NPV VaR and base their decision on that selection. If in running a scenario, the net NPV was to the left of the 99th percentile target

Table 4 Brand Company NPV Scenarios

Scenario	Baseline	Comparison	CM Cost Volatility	Profit Margin Volatility	Hedge Cost	US Tax Rate
1	US Batch	US CM	2.50%	0	0	21%
2	US Batch	US CM	10%	0	0	21%
3	US Batch	US CM	15%	0	0	21%
4	US Batch	US CM	2.50%	15%(Yrs 1-12)/10%(Yrs 13-20)	0	21%
5	US Batch	US CM	2.50%	10%(Yrs 1-12)/5%(Yrs 13-20)	0	21%
6	US Batch	US CM	2.50%	5%(Yrs 1-12)/0%(Yrs 13-20)	0	21%
7	US CM	China Batch	2.50%	0%	1%	21%
8	US CM	China Batch	2.50%	0%	2%	21%
9	US CM	China Batch	2.50%	0%	4%	21%
10	US CM	China Batch	10.00%	0%	1%	21%
11	US CM	China Batch	10.00%	0%	2%	21%
12	US CM	China Batch	10.00%	0%	4%	21%
13	US CM	China Batch	15.00%	0%	1%	21%
14	US CM	China Batch	15.00%	0%	2%	21%
15	US CM	China Batch	15.00%	0%	4%	21%
16	US CM	China Batch	2.50%	0%	1%	28%
17	US CM	China Batch	2.50%	0%	2%	28%
18	US CM	China Batch	2.50%	0%	4%	28%
19	US CM	China Batch	10.00%	0%	1%	28%
20	US CM	China Batch	10.00%	0%	2%	28%
21	US CM	China Batch	10.00%	0%	4%	28%
22	US CM	China Batch	15.00%	0%	1%	28%
23	US CM	China Batch	15.00%	0%	2%	28%
24	US CM	China Batch	15.00%	0%	4%	28%
25	US Batch	China Batch	2.50%	0%	1%	21%
26	US Batch	China Batch	2.50%	0%	2%	21%
27	US Batch	China Batch	2.50%	0%	4%	21%
28	US Batch	China Batch	2.50%	0%	1%	28%
29	US Batch	China Batch	2.50%	0%	2%	28%
30	US Batch	China Batch	2.50%	0%	4%	28%
31	US CM	India Batch	2.50%	0%	1%	21%
32	US CM	India Batch	2.50%	0%	2%	21%
33	US CM	India Batch	2.50%	0%	4%	21%
34	US CM	India Batch	10.00%	0%	1%	21%
35	US CM	India Batch	10.00%	0%	2%	21%
36	US CM	India Batch	10.00%	0%	4%	21%
37	US CM	India Batch	15.00%	0%	1%	21%
38	US CM	India Batch	15.00%	0%	2%	21%
39	US CM	India Batch	15.00%	0%	4%	21%
40	US CM	India Batch	2.50%	0%	1%	28%
41	US CM	India Batch	2.50%	0%	2%	28%
42	US CM	India Batch	2.50%	0%	4%	28%
43	US CM	India Batch	10.00%	0%	1%	28%
44	US CM	India Batch	10.00%	0%	2%	28%
45	US CM	India Batch	10.00%	0%	4%	28%
46	US CM	India Batch	15.00%	0%	1%	28%
47	US CM	India Batch	15.00%	0%	2%	28%
48	US CM	India Batch	15.00%	0%	4%	28%
49	US Batch	India Batch	2.50%	0%	1%	21%
50	US Batch	India Batch	2.50%	0%	2%	21%
51	US Batch	India Batch	2.50%	0%	4%	21%
52	US Batch	India Batch	2.50%	0%	1%	28%
53	US Batch	India Batch	2.50%	0%	2%	28%
54	US Batch	India Batch	2.50%	0%	4%	28%
55	US CM	Ireland Batch	2.50%	0%	1%	21%
56	US CM	Ireland Batch	2.50%	0%	2%	21%
57	US CM	Ireland Batch	2.50%	0%	4%	21%
58	US CM	Ireland Batch	10.00%	0%	1%	21%
59	US CM	Ireland Batch	10.00%	0%	2%	21%
60	US CM	Ireland Batch	10.00%	0%	4%	21%
61	US CM	Ireland Batch	15.00%	0%	1%	21%
62	US CM	Ireland Batch	15.00%	0%	2%	21%
63	US CM	Ireland Batch	15.00%	0%	4%	21%
64	US CM	Ireland Batch	2.50%	0%	1%	28%
65	US CM	Ireland Batch	2.50%	0%	2%	28%
66	US CM	Ireland Batch	2.50%	0%	4%	28%
67	US CM	Ireland Batch	10.00%	0%	1%	28%
68	US CM	Ireland Batch	10.00%	0%	2%	28%
69	US CM	Ireland Batch	10.00%	0%	4%	28%
70	US CM	Ireland Batch	15.00%	0%	1%	28%
71	US CM	Ireland Batch	15.00%	0%	2%	28%
72	US CM	Ireland Batch	15.00%	0%	4%	28%
73	US Batch	Ireland Batch	2.50%	0%	1%	21%
74	US Batch	Ireland Batch	2.50%	0%	2%	21%
75	US Batch	Ireland Batch	2.50%	0%	4%	21%
76	US Batch	Ireland Batch	2.50%	0%	1%	28%
77	US Batch	Ireland Batch	2.50%	0%	2%	28%
78	US Batch	Ireland Batch	2.50%	0%	4%	28%

Table 5 Generic Company NPV Scenarios

Scenario	Baseline	Comparison	CM Cost Volatility	Profit Margin Volatility	Hedge Cost	US Tax Rate
1	US Batch	US CM	2.50%	0	0	21%
2	US Batch	US CM	10%	0	0	21%
3	US Batch	US CM	15%	0	0	21%
4	US Batch	US CM	2.50%	10%(Yrs 1-20)	0	21%
5	US Batch	US CM	2.50%	5%(Yrs 1-20)	0	21%
6	US Batch	US CM	2.50%	0%(Yrs 1-20)	0	21%
7	US CM	China Batch	2.50%	0%	1%	21%
8	US CM	China Batch	2.50%	0%	2%	21%
9	US CM	China Batch	2.50%	0%	4%	21%
10	US CM	China Batch	10.00%	0%	1%	21%
11	US CM	China Batch	10.00%	0%	2%	21%
12	US CM	China Batch	10.00%	0%	4%	21%
13	US CM	China Batch	15.00%	0%	1%	21%
14	US CM	China Batch	15.00%	0%	2%	21%
15	US CM	China Batch	15.00%	0%	4%	21%
16	US CM	China Batch	2.50%	0%	1%	28%
17	US CM	China Batch	2.50%	0%	2%	28%
18	US CM	China Batch	2.50%	0%	4%	28%
19	US CM	China Batch	10.00%	0%	1%	28%
20	US CM	China Batch	10.00%	0%	2%	28%
21	US CM	China Batch	10.00%	0%	4%	28%
22	US CM	China Batch	15.00%	0%	1%	28%
23	US CM	China Batch	15.00%	0%	2%	28%
24	US CM	China Batch	15.00%	0%	4%	28%
25	US Batch	China Batch	2.50%	0%	1%	21%
26	US Batch	China Batch	2.50%	0%	2%	21%
27	US Batch	China Batch	2.50%	0%	4%	21%
28	US Batch	China Batch	2.50%	0%	1%	28%
29	US Batch	China Batch	2.50%	0%	2%	28%
30	US Batch	China Batch	2.50%	0%	4%	28%
31	US CM	India Batch	2.50%	0%	1%	21%
32	US CM	India Batch	2.50%	0%	2%	21%
33	US CM	India Batch	2.50%	0%	4%	21%
34	US CM	India Batch	10.00%	0%	1%	21%
35	US CM	India Batch	10.00%	0%	2%	21%
36	US CM	India Batch	10.00%	0%	4%	21%
37	US CM	India Batch	15.00%	0%	1%	21%
38	US CM	India Batch	15.00%	0%	2%	21%
39	US CM	India Batch	15.00%	0%	4%	21%
40	US CM	India Batch	2.50%	0%	1%	28%
41	US CM	India Batch	2.50%	0%	2%	28%
42	US CM	India Batch	2.50%	0%	4%	28%
43	US CM	India Batch	10.00%	0%	1%	28%
44	US CM	India Batch	10.00%	0%	2%	28%
45	US CM	India Batch	10.00%	0%	4%	28%
46	US CM	India Batch	15.00%	0%	1%	28%
47	US CM	India Batch	15.00%	0%	2%	28%
48	US CM	India Batch	15.00%	0%	4%	28%
49	US Batch	India Batch	2.50%	0%	1%	21%
50	US Batch	India Batch	2.50%	0%	2%	21%
51	US Batch	India Batch	2.50%	0%	4%	21%
52	US Batch	India Batch	2.50%	0%	1%	28%
53	US Batch	India Batch	2.50%	0%	2%	28%
54	US Batch	India Batch	2.50%	0%	4%	28%
55	US CM	Ireland Batch	2.50%	0%	1%	21%
56	US CM	Ireland Batch	2.50%	0%	2%	21%
57	US CM	Ireland Batch	2.50%	0%	4%	21%
58	US CM	Ireland Batch	10.00%	0%	1%	21%
59	US CM	Ireland Batch	10.00%	0%	2%	21%
60	US CM	Ireland Batch	10.00%	0%	4%	21%
61	US CM	Ireland Batch	15.00%	0%	1%	21%
62	US CM	Ireland Batch	15.00%	0%	2%	21%
63	US CM	Ireland Batch	15.00%	0%	4%	21%
64	US CM	Ireland Batch	2.50%	0%	1%	28%
65	US CM	Ireland Batch	2.50%	0%	2%	28%
66	US CM	Ireland Batch	2.50%	0%	4%	28%
67	US CM	Ireland Batch	10.00%	0%	1%	28%
68	US CM	Ireland Batch	10.00%	0%	2%	28%
69	US CM	Ireland Batch	10.00%	0%	4%	28%
70	US CM	Ireland Batch	15.00%	0%	1%	28%
71	US CM	Ireland Batch	15.00%	0%	2%	28%
72	US CM	Ireland Batch	15.00%	0%	4%	28%
73	US Batch	Ireland Batch	2.50%	0%	1%	21%
74	US Batch	Ireland Batch	2.50%	0%	2%	21%
75	US Batch	Ireland Batch	2.50%	0%	4%	21%
76	US Batch	Ireland Batch	2.50%	0%	1%	28%
77	US Batch	Ireland Batch	2.50%	0%	2%	28%
78	US Batch	Ireland Batch	2.50%	0%	4%	28%

then the project would be less desirable. Note that the company can select any percentile for their target VaR and so a less restrictive target such as a 95th percentile net NPV could be used instead, depending on the company's tolerance for investment risk.

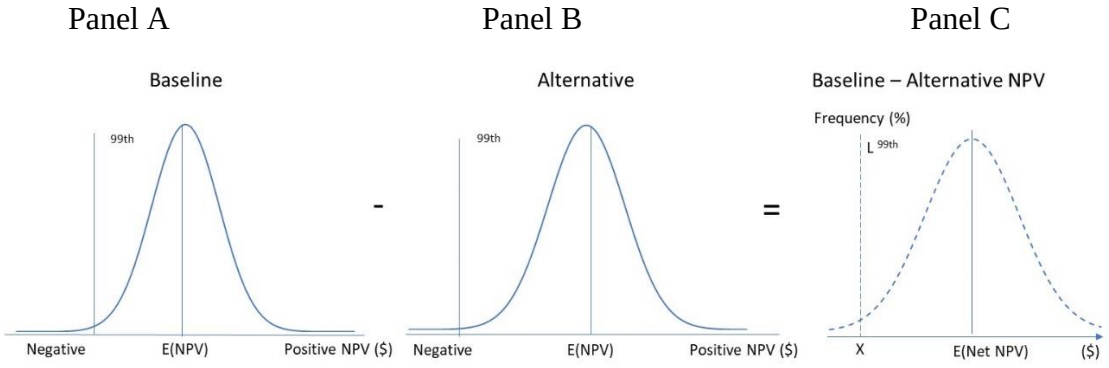
For the analysis a set of hypotheses of interest comparing U.S. to three NonU.S. sites using CM technology or batch are as follows:

1. For U.S. manufacturing sites, Brand Company $E(NPV_{CM}) - E(NPV_{Batch}) > 0$
2. For U.S. manufacturing sites, Generic Company $E(NPV_{CM}) - E(NPV_{Batch}) < 0$
3. For U.S. versus other country sites, Brand Company $E\left(NPV_{Batch}^{US}\right) - E\left(NPV_{Batch}^{NonUS}\right) < 0$
4. For U.S. versus other country sites, Generic Company $E\left(NPV_{Batch}^{US}\right) - E\left(NPV_{Batch}^{NonUS}\right) < 0$
5. For U.S. versus other country sites, Brand Company $E\left(NPV_{CM}^{US}\right) - E\left(NPV_{Batch}^{NonUS}\right) > 0$
6. For U.S. versus other country sites, Generic Company $E\left(NPV_{CM}^{US}\right) - E\left(NPV_{Batch}^{NonUS}\right) < 0$

Table 6 Key Country Assumptions

Country	Manufacturing Cost Index[58]	Corporate Marginal Tax Rate[59]
United States	100	21%
China	96	25%
India	87	30%
Ireland	91	12.5%

Figure 7 Investment VaR and Net NPV Concept



Hypothesis 1 is based on the proposition that the lower cost of CM technology along with higher profit margins with lower variability in those margins will generate positive net NPV for CM

[58] BCG, How Shifting Costs are Altering the Math of Global Manufacturing, December 11, 2018.
[59] Tax Foundation, Corporate Tax Rates Around the World, 2020.

over batch technology for brand companies in the U.S. However, it is hypothesized that lower CM costs may not be sufficient to offset the lower profit margins of generic companies and higher cost variability of CM (Hypothesis 2). Hypotheses 3 and 4 reflects a view that differential costs and tax rates will make foreign investment in batch technology a preferred investment choice over investment in batch technology in the U.S. regardless of company type. Finally, Hypotheses 5 and 6 reflect a view that lower costs of CM technology in the U.S. will offset any tax and cost advantages overseas for brand companies but not for generics, again reflecting differences in profitability and markets for those companies.

Results and Implications

Figure 8 provides a summary of the comparison for brand companies deciding whether to manufacture in the U.S. leveraging CM versus batch technology under the 3 CM cost volatility scenarios. The results support Hypothesis 1 that for brand companies, NPV for CM-based technology is greater than that using a batch process across all cost volatility scenarios.[60] Moreover, it should be noted that only under the most extreme cost volatility (15%) scenario and most conservative investment VaR (99th percentile) would batch NPV ever exceed CM NPV (see Appendix tables). This suggests that at least for U.S. sites, CM manufacturing should be the preferred technology choice for brand companies. These results also hold up when looking across profit margin scenarios for brand companies as shown in Figure 9. In all scenarios, expected and tail risk net NPVs remain positive, corroborating the cost volatility scenario results above.

Turning next to generic company manufacturing investment alternatives, Hypothesis 2 is not supported by the NPV findings (Figure 10). For all CM cost volatility scenarios, CM maintains a positive net E(NPV) over batch processing technology. And with the exception of the 99th percentile outcome under a 15% CM cost volatility scenario, CM dominates batch in the tail of the NPV distribution as well. While generic companies experience a much more competitive environment than brand companies, the cost reduction associated with CM appears to still provide an advantage over more costly batch processes for generic companies. This result is confirmed further in Figure 11 that shows positive E(NPV) over all profit margin scenarios. And none of the net NPV tail risk scenarios are negative, suggesting that even for generic companies, CM technology would be preferred over batch on an NPV basis.

To investigate U.S. competitiveness with other key countries manufacturing pharmaceutical products, an NPV comparison of investing in batch processes in the U.S. versus China, India or

[60] It should be pointed out that a reason why E(NPV) is nonmonotonic for both CM and batch results in cost volatility is explained by the fact that a different set of random numbers were generated for each volatility scenario so some small differences could arise as a result.

Figure 8 Brand Company U.S. Site Technology NPV Comparisons by Cost Volatility Scenarios

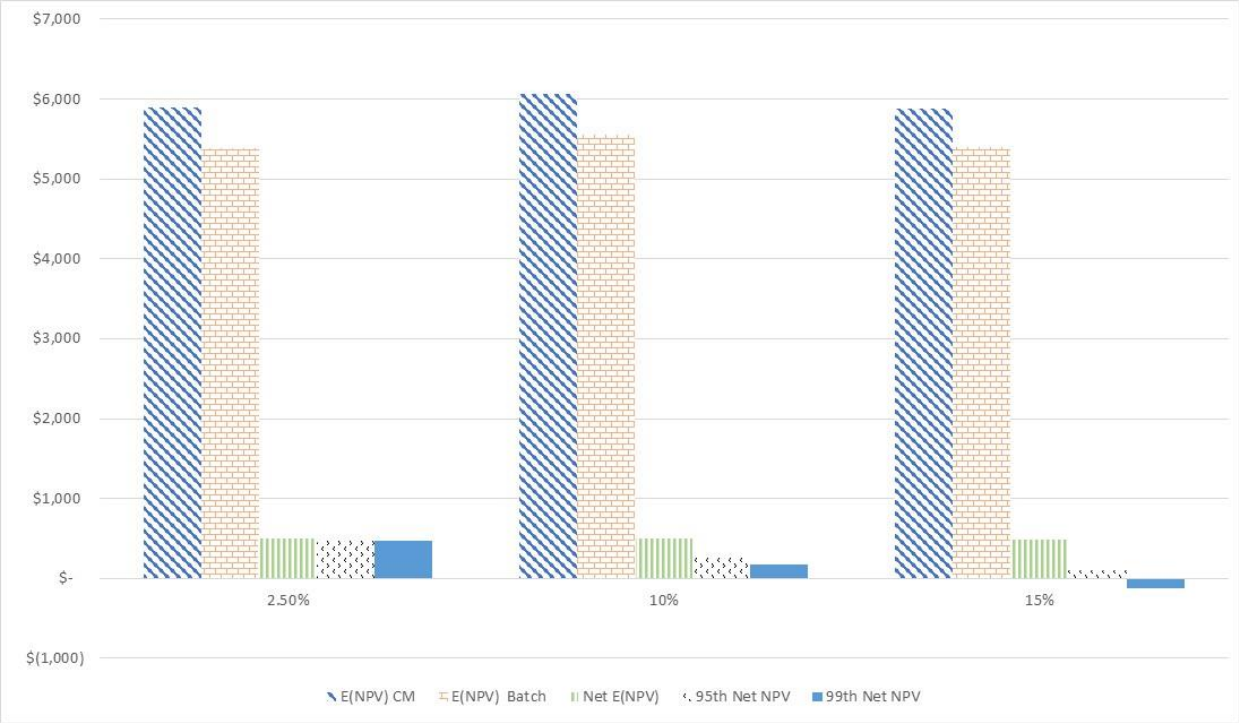


Figure 9 Brand Company U.S. Site Technology NPV Comparisons by Profit Margin Scenarios

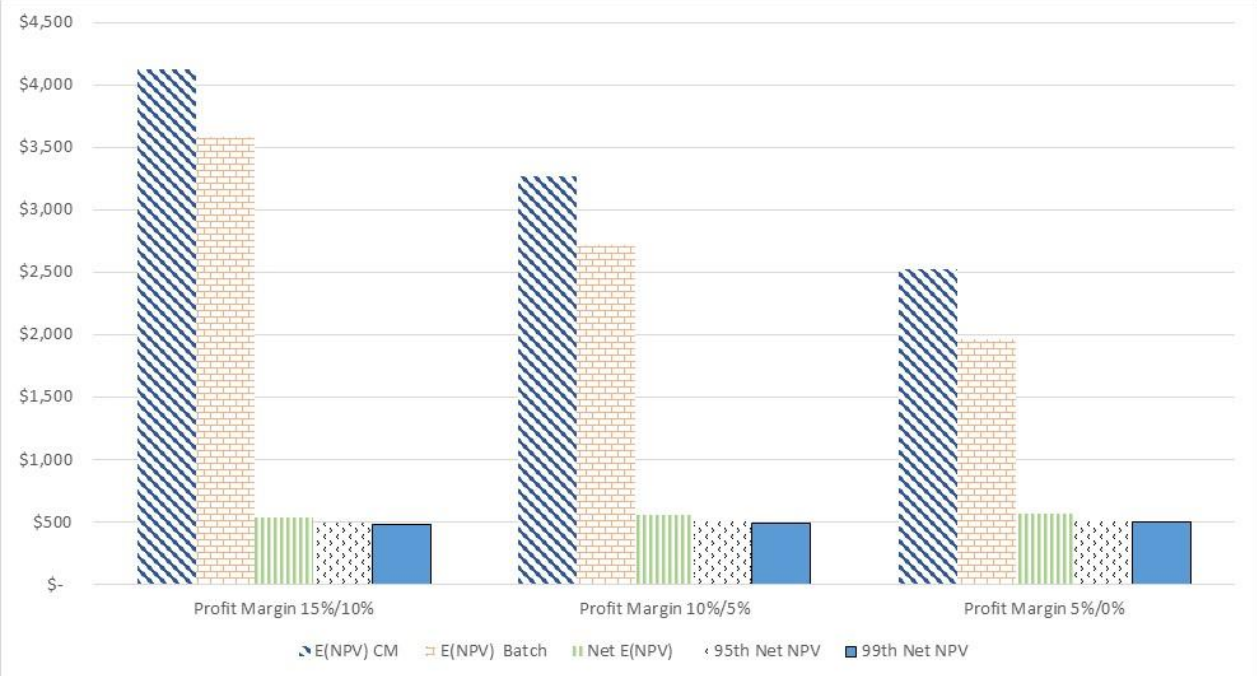
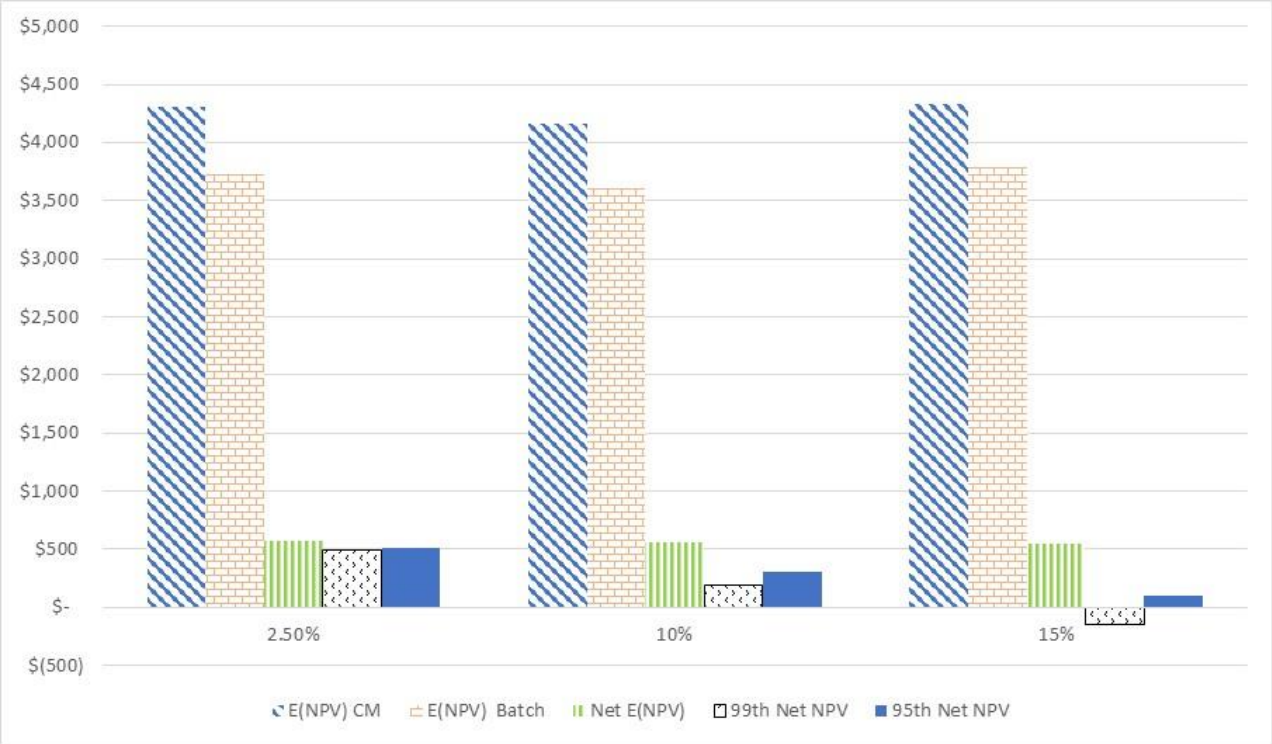


Figure 10 Generic Company U.S. Site Technology NPV Comparisons by Cost Volatility Scenarios

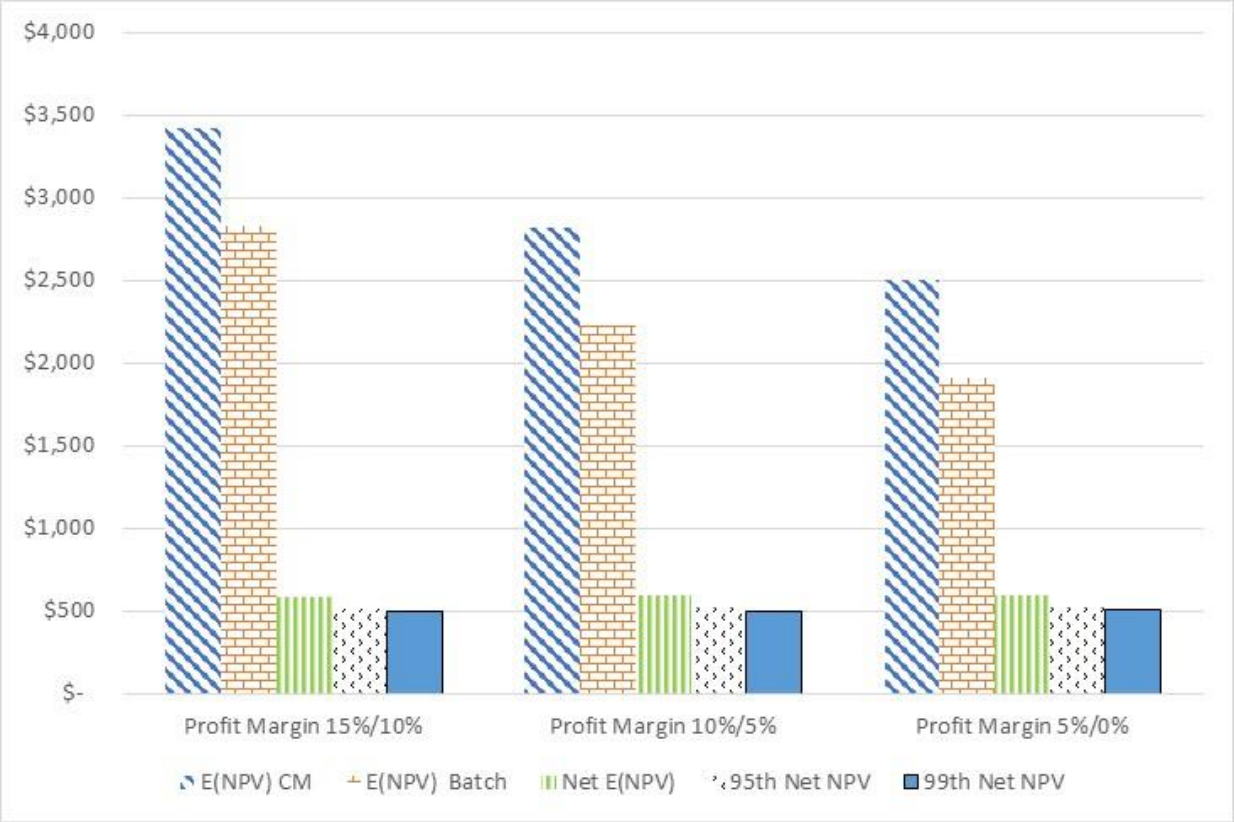


Ireland was made. The results from this analysis are found in Figures 12 and 13 for brand and generic companies, respectively. The baseline tax scenario assumed U.S. marginal corporate tax rates of 21% under the foreign exchange hedge costs scenarios noted previously for the other countries.

The results indicate that compared to investing in batch technology in China and India, investing in batch technology in the U.S. would result in net positive E(NPV) across all hedge cost scenarios. For the China and India scenarios, net NPVs at the 95th percentile are positive as well. These results suggest that under current U.S. tax policy, investment in U.S. pharmaceutical manufacturing using batch technology would generate higher expected net NPVs than in China or India and under more extreme outcomes as well. The fact that investment in batch technology in the U.S. would generate higher expected NPV over investment in the same technology on China or India suggests that relative costs, tax policy and market conditions may already favor U.S. pharmaceutical manufacturing investment.

The results, however, are much different when considering Ireland as a manufacturing site. Due to much lower corporate tax rates than the U.S. (21%), Ireland (12.5%) enjoys an advantage that

Figure 11 Generic Company U.S. Site Technology NPV Comparisons by Profit Margin Scenarios

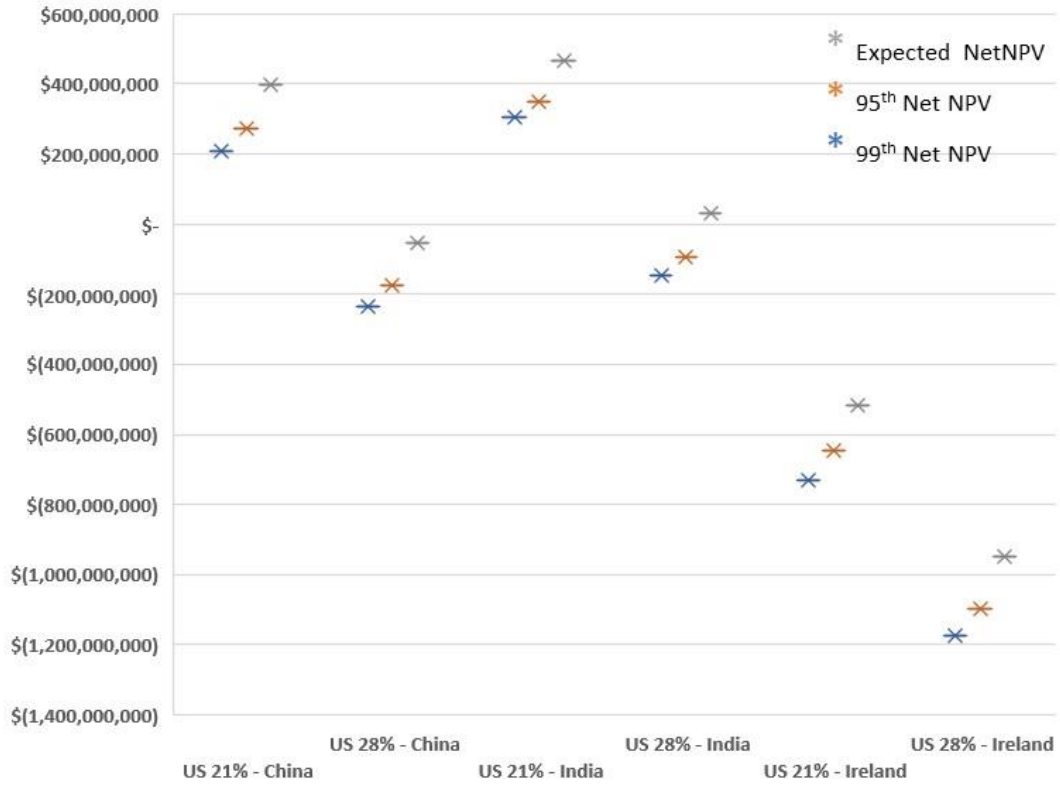


results in negative net E(NPV) for all hedging cost scenarios.[61] These results underscore the importance of tax policy in manufacturing decisions absent technology as a factor of production.

Another set of scenarios were run assuming an increase in U.S. corporate tax rates to 28% to better understand how changes in tax policy would affect decisions to invest in domestic pharmaceutical manufacturing facilities. Corporate investment decisions are affected by a host of financial and nonfinancial factors including differential corporate tax rates across the world. Applying a 28% corporate tax to U.S. pharmaceutical manufacturing investments would lead to negative net NPVs for both brand and generic companies in the U.S. to China scenarios. And increasing corporate tax rates in the U.S. to 28% would drastically reduce net NPV outcomes compared to investing in India under a 21% U.S. corporate tax scenario. These results have

[61] A proposal supported by 130 countries to establish a global minimum corporate tax rate of 15% in 2021 introduces some tax policy uncertainty into global corporate tax rates going forward. OECD/G20 Base Erosion and Profit Shifting Project, Statement on a Two-Pillar Solution to Address the Tax Challenges Arising from the Digitalisation of the Economy, July 1, 2021.

Figure 12 Brand Company Batch Investment Net E(NPV) in the U.S. vs. NonUS Sites



major implications for redirecting pharmaceutical manufacturing to the U.S. The results overall comparing U.S. to nonU.S. investment for batch technology are contrary to Hypotheses 3 and 4 under current U.S. tax rates but corroborate these hypotheses for the China scenarios if U.S. tax rates rose to 28%.[62]

To test Hypotheses 5 and 6, a number of scenarios were generated comparing investment in CM technology in the U.S. to batch technology in China, India or Ireland assuming a 21% U.S. corporate tax rate and all CM cost volatility and hedge cost scenarios. The results from those scenarios are summarized in Figures 14 and 15. Not surprising given their substantially lower costs than batch, CM technology investment in the U.S. generates a positive net E(NPV) compared against batch technology investment in China or India. All but two (three) of the nine scenarios generate positive net NPVs at the 99th percentile for brand (generic) companies in the China scenarios. Between a third to about half of the India scenarios result in positive net NPVs at the 99th percentile. Even taking into account CM's lower costs, investing in U.S. CM manufacturing still is not as attractive on an expected net NPV basis as investing in batch

[62] Note that state and local taxes were not taken into consideration in the analysis which could further affect US competitiveness.

Figure 13 Generic Company Batch Investment Net E(NPV) in the U.S. vs. NonUS Sites

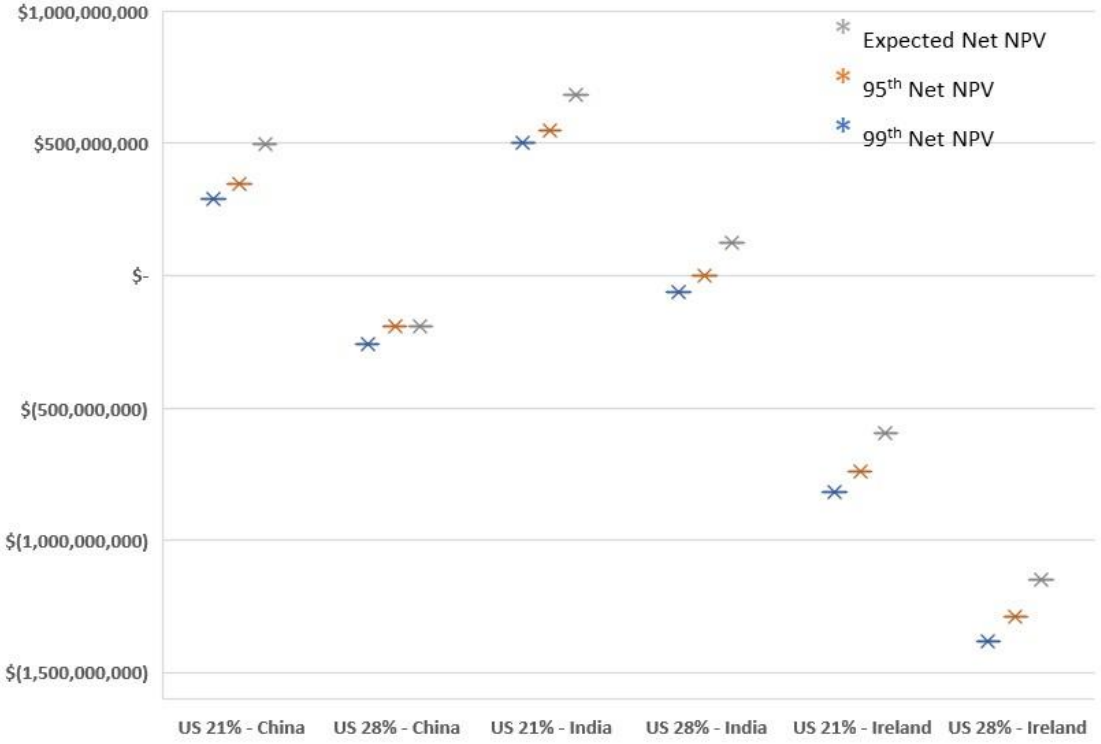


Figure 14 Brand Company U.S. CM vs NonUS Batch Investment Net E(NPV)

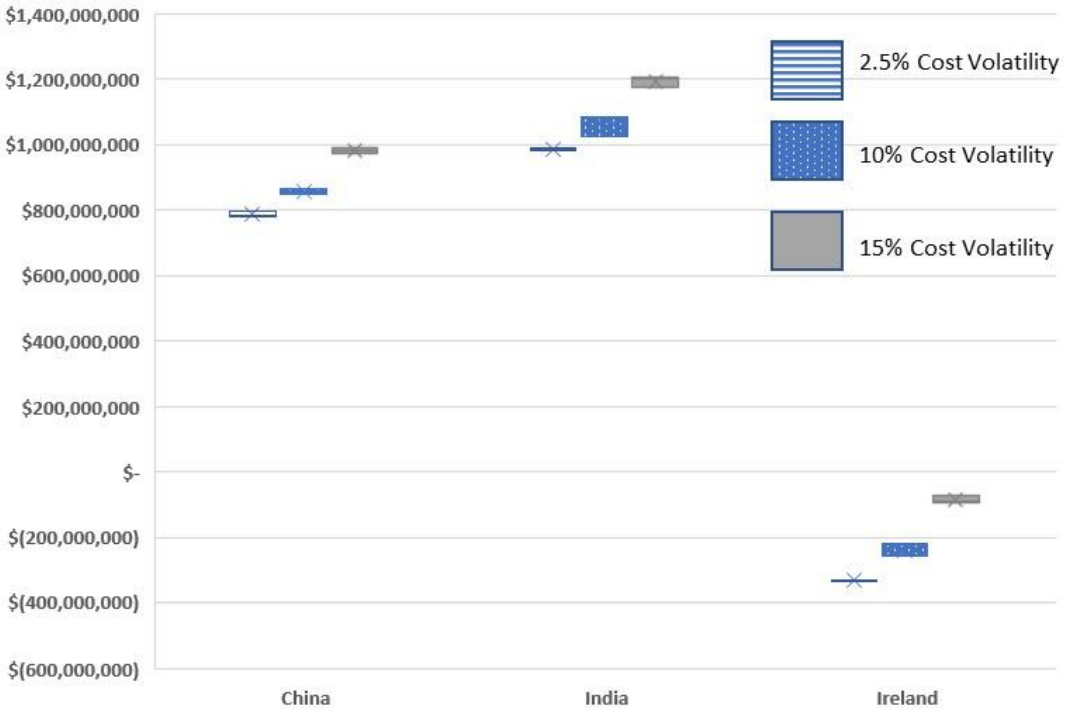
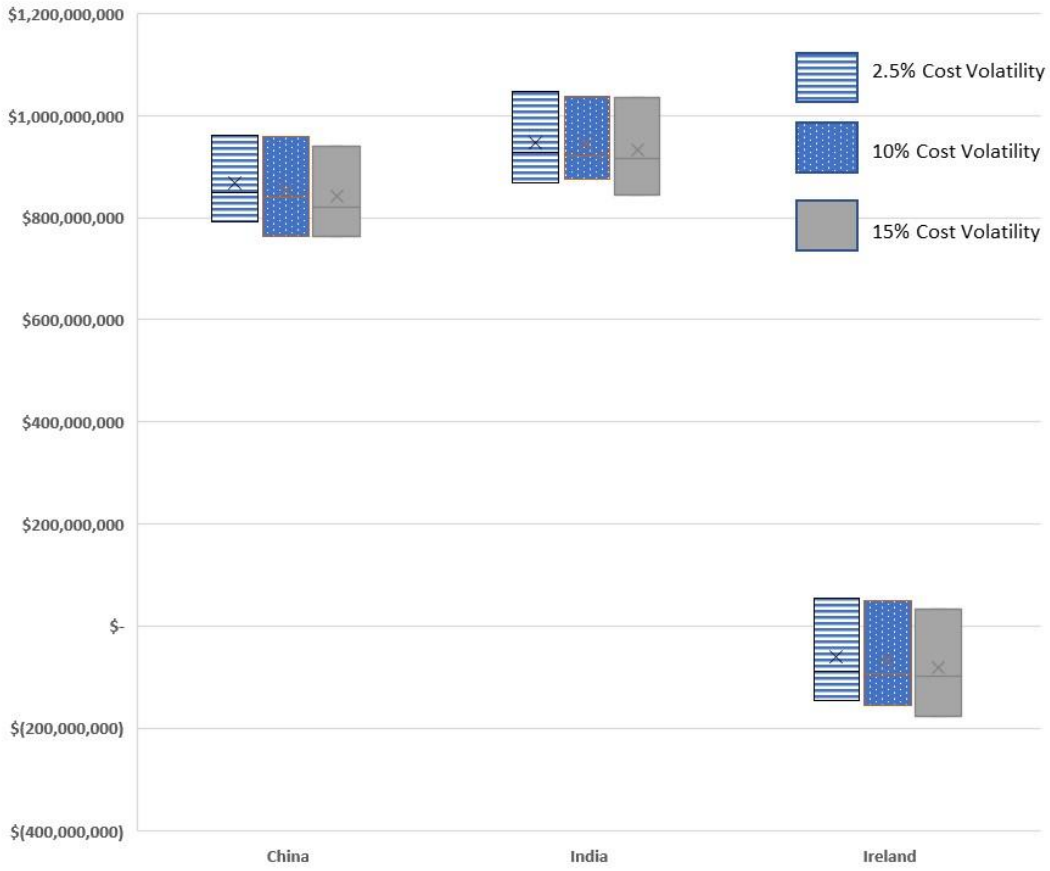


Figure 15 Generic Company U.S. CM vs NonUS Batch Investment Net E(NPV)



processing in Ireland. The combination of lower manufacturing costs and tax rates in Ireland appear to be driving these results. Finally, for scenarios applying a possible 28% U.S. corporate tax rate, CM manufacturing in the U.S. versus batch processing in China or India is less attractive as expected net NPV declines compared to the 21% U.S. tax rate scenarios.

Business Implications

The results of the NPV simulations have important implications for pharmaceutical company investment in CM manufacturing technology over current batch processing as well as for domestic versus foreign investment. The major findings are summarized as follows:

Finding 1:

When looking at comparing investment in either CM or batch for a new U.S. facility, the results clearly suggest that the lower costs associated with CM technology should lead to both brand and generic companies investing in the more CM manufacturing technology. While the result

conformed to expectations for brand companies based on their larger and less volatile profit margins, it was somewhat surprising for generic companies, taking into account scenarios where CM cost volatility was increased substantially beyond the baseline batch cost volatility.

Finding 2:

The simulation analysis demonstrated that under current U.S. tax rates, investing in batch technology at U.S. sites would be economically more attractive than investing in batch technology in China or India. Somewhat lower manufacturing costs in these countries appear to be insufficient offsets to foreign exchange hedging costs and lower corporate tax rates in the US. However, much lower tax rates in Ireland make that country extremely competitive relative to the U.S. such that despite lower CM costs, investing in batch processing in Ireland provides higher NPV to both brand and generic companies across scenarios.

Finding 3:

Investing in CM technology in the U.S. under current tax rates results in positive expected net NPVs over batch technology investments in China or India for both brand and generic companies. Lower U.S. corporate tax rates, and CM manufacturing costs along with no hedging costs in the U.S. scenarios drive those results.

Finding 4:

U.S. tax policy has a material impact on whether pharmaceutical companies would decide to invest on the U.S. or not for their manufacturing. When U.S. corporate tax rates were raised from 21% to 28%, it turned expected net NPVs negative for batch and reduced them for CM technology in the U.S. versus investing in batch processing in China.

The results demonstrate the potential for CM to make domestic manufacturing of pharmaceuticals more economically attractive than foreign manufacturing of those products. However, the results do not comport with actual experience. That is, very little investment in CM-based pharmaceutical manufacturing has taken place thus far and most of that investment has been by large brand companies. Further, there is no indication that the industry has refocused much of their manufacturing investments toward the U.S. This raises serious questions regarding barriers and/or risks that may be preventing these companies from adopting advanced technologies for U.S. pharmaceutical manufacturing.

Factors likely to be driving a lack of investment in CM pharmaceutical manufacturing technology in the U.S. include the following:

- Lack of solid data on CM investment and operating costs that raises investment uncertainty.
- Potential management bias toward proven technology
- Manufacturing overcapacity
- Relative high cost of plant retrofitting due to large amounts of undepreciated manufacturing assets
- Potential lack of skilled labor to operate advanced manufacturing technology
- Market factors that favor greater focus on R&D investment over manufacturing investment
- Regulatory uncertainty regarding product approval leveraging advanced manufacturing processes
- More stringent environmental regulations in the U.S.
- Differential corporate tax rates between the U.S. and other countries
- A large percentage of API manufacturing outside the U.S. that can affect finished dosage form end products due to supply chain logistics

It will not be sufficient to merely demonstrate financial feasibility of advanced manufacturing technologies given long standing industry structural, economic and attitudinal issues that have dampened interest in adopting advanced manufacturing technology in the industry thus far. Crafting public policies to address such industry barriers and risks to domestic and advanced technology pharmaceutical manufacturing investment will be essential in ultimately stimulating such investments.

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Appendix: Supplementary Simulation Analysis Tables

Table A1: US Manufacturing CM and Batch NPV Scenarios

Brand		CM Manufacturing		Batch Manufacturing		CM_Batch Manufacturing	
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
CM Cost Volalatility Scenarios (21% tax rate)									
US 2.5%CM 2.5% Batch	$ 5,889,126,452	$ (1,193,720,527)	$ (2,444,790,761)	$ 5,378,012,287	$ (1,732,711,728)	$ (3,017,496,506)	$ 511,114,165	$ 478,504,162	$ 468,880,409
US 10%CM 2.5% Batch	$ 6,058,615,758	$ (1,280,415,594)	$ (2,494,368,492)	$ 5,557,290,991	$ (1,778,787,449)	$ (2,989,364,027)	$ 501,324,768	$ 278,600,187	$ 170,112,177
US 15%CM 2.5% Batch	$ 5,887,513,945	$ (1,291,694,017)	$ (2,490,918,394)	$ 5,398,446,062	$ (1,803,373,330)	$ (2,991,792,404)	$ 489,067,883	$ 97,304,450	$ (128,870,986)
Profit Margin Scenarios (21% tax rate)									
Profit Margin (PM) 15% (Yrs. 1-12)/ PM 10% (Yrs. 13-20)	$ 4,119,708,374	$ (2,512,441,326)	$ (3,648,496,875)	$ 3,579,208,017	$ (3,104,378,647)	$ (4,269,335,385)	$ 540,500,357	$ 493,207,614	$ 479,724,836
Profit Margin (PM) 10% (Yrs. 1-12)/ PM 15% (Yrs. 13-20)	$ 3,269,927,243	$ (3,019,433,469)	$ (4,082,868,227)	$ 2,717,689,363	$ (3,627,875,662)	$ (4,700,898,923)	$ 552,237,880	$ 504,522,200	$ 489,444,609
Profit Margin (PM) 5% (Yrs. 1-12)/ PM 0% (Yrs. 13-20)	$ 2,528,110,100	$ (3,520,878,410)	$ (4,510,893,247)	$ 1,966,515,030	$ (4,138,619,009)	$ (5,146,219,541)	$ 561,595,069	$ 511,291,341	$ 499,181,436
Generic									
CM Cost Volalatility Scenarios (21% tax rate)									
US 2.5%CM 2.5% Batch	$ 4,303,961,171	$ (3,587,371,501)	$ (4,673,752,873)	$ 3,727,087,162	$ (4,233,134,591)	$ (5,327,928,913)	$ 576,874,009	$ 509,763,665	$ 495,116,700
US 10%CM 2.5% Batch	$ 4,164,924,240	$ (3,538,517,679)	$ (4,667,902,667)	$ 3,600,156,478	$ (4,189,304,776)	$ (5,226,468,243)	$ 564,767,761	$ 308,484,270	$ 189,469,083
US 15%CM 2.5% Batch	$ 4,337,051,710	$ (3,634,214,355)	$ (4,710,852,708)	$ 3,789,166,657	$ (4,177,269,008)	$ (5,296,651,811)	$ 547,885,053	$ 98,698,872	$ (151,148,504)
Profit Margin Scenarios (21% tax rate)									
PM 10% (Yrs. 1-20)	$ 3,417,289,605	$ (3,785,696,503)	$ (4,807,195,181)	$ 2,833,575,812	$ (4,433,448,747)	$ (5,453,091,203)	$ 583,713,793	$ 514,062,619	$ 497,692,248
PM 5% (Yrs. 1-20)	$ 2,819,842,911	$ (3,972,163,892)	$ (4,929,190,362)	$ 2,231,424,185	$ (4,619,702,621)	$ (5,564,553,513)	$ 588,418,726	$ 519,269,058	$ 501,126,286
PM 0% (Yrs. 1-20)	$ 2,502,586,207	$ (4,165,478,057)	$ (5,138,287,668)	$ 1,910,558,036	$ (4,809,157,924)	$ (5,775,162,807)	$ 592,028,170	$ 523,335,710	$ 503,014,492

Table A2: US/Non US Brand Manufacturing Batch NPV Scenarios

	US Manufacturing			Non US Manufacturing			US - Non US Manufacturing		
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
US Batch wih China Batch									
China 2.5%Batch hedge 1% tax(21%)	$ 5,533,183,425	$ (1,803,442,079)	$ (2,931,542,601)	$ 5,242,509,211	$ (1,772,240,064)	$ (2,870,844,970)	$ 290,674,215	$ (40,152,304)	$ (65,795,859)
China 2.5%Batch hedge 2% tax(21%)	$ 5,394,678,151	$ (1,760,314,183)	$ (2,997,491,722)	$ 5,047,143,182	$ (1,763,399,391)	$ (2,984,245,340)	$ 347,534,969	$ (12,984,384)	$ (38,639,995)
China 2.5%Batch hedge 4% tax(21%)	$ 5,590,066,203	$ (1,781,292,078)	$ (2,991,516,201)	$ 5,095,150,933	$ (1,858,925,020)	$ (3,042,018,522)	$ 494,915,270	$ 39,970,610	$ 5,959,368
China 2.5%Batch hedge 1% tax(28%)	$ 4,859,371,133	$ (1,868,847,199)	$ (3,041,840,645)	$ 5,117,532,712	$ (1,775,200,335)	$ (2,957,652,168)	$ (258,161,579)	$ (643,260,979)	$ (1,217,077,851)
China 2.5%Batch hedge 2% tax(28%)	$ 4,922,151,616	$ (1,813,797,515)	$ (2,990,691,247)	$ 5,116,076,796	$ (1,750,664,164)	$ (2,939,261,727)	$ (193,925,180)	$ (465,133,512)	$ (853,593,861)
China 2.5%Batch hedge 4% tax(28%)	$ 4,994,878,104	$ (1,831,014,522)	$ (2,936,244,458)	$ 5,057,178,903	$ (1,831,248,444)	$ (2,954,900,143)	$ (62,300,799)	$ (88,513,105)	$ (91,612,920)
US Batch wih India Batch									
India 2.5%Batch hedge 1% tax(21%)	$ 5,603,423,724	$ (1,820,000,453)	$ (2,964,488,002)	$ 5,099,894,011	$ (1,623,330,044)	$ (2,702,058,270)	$ 503,529,713	$ (216,655,641)	$ (283,853,652)
India 2.5%Batch hedge 2% tax(21%)	$ 5,458,172,771	$ (1,816,157,642)	$ (2,991,335,940)	$ 4,910,691,572	$ (1,652,770,673)	$ (2,751,388,833)	$ 547,481,199	$ (187,808,601)	$ (254,784,530)
India 2.5%Batch hedge 4% tax(21%)	$ 5,529,372,057	$ (1,794,809,978)	$ (3,006,220,676)	$ 4,848,295,889	$ (1,693,483,818)	$ (2,847,035,797)	$ 681,076,167	$ (133,205,414)	$ (202,330,506)
India 2.5%Batch hedge 1% tax(28%)	$ 4,916,802,845	$ (1,835,358,788)	$ (3,008,379,681)	$ 4,978,621,287	$ (1,564,252,735)	$ (2,709,570,912)	$ (61,818,442)	$ (270,400,265)	$ (306,829,062)
India 2.5%Batch hedge 2% tax(28%)	$ 4,879,120,595	$ (1,848,421,054)	$ (2,981,311,353)	$ 4,878,377,389	$ (1,611,802,091)	$ (2,742,449,319)	$ 743,206	$ (244,753,964)	$ (279,978,543)
India 2.5%Batch hedge 4% tax(28%)	$ 4,861,265,906	$ (1,828,938,161)	$ (2,998,401,007)	$ 4,737,090,384	$ (1,662,148,327)	$ (2,797,366,480)	$ 124,175,522	$ (193,814,650)	$ (232,952,448)
US Batch wih Ireland Batch									
Ireland 2.5%Batch hedge 1% tax(21%)	$ 5,473,819,214	$ (1,729,662,068)	$ (2,987,731,562)	$ 6,293,423,435	$ (1,437,516,968)	$ (2,735,859,720)	$ (819,604,221)	$ (2,166,594,058)	$ (4,203,926,169)
Ireland 2.5%Batch hedge 2% tax(21%)	$ 5,428,135,206	$ (1,806,259,764)	$ (2,919,133,701)	$ 6,168,345,007	$ (1,550,714,233)	$ (2,704,558,683)	$ (740,209,801)	$ (1,942,559,069)	$ (3,664,005,725)
Ireland 2.5%Batch hedge 4% tax(21%)	$ 5,533,155,680	$ (1,774,701,921)	$ (2,890,235,023)	$ 6,126,834,762	$ (1,576,827,870)	$ (2,747,595,141)	$ (593,679,081)	$ (1,554,961,045)	$ (2,813,826,776)
Ireland 2.5%Batch hedge 1% tax(28%)	$ 4,990,474,552	$ (1,849,778,829)	$ (3,009,893,424)	$ 6,370,761,520	$ (1,490,271,339)	$ (2,738,587,745)	$ (1,380,286,968)	$ (3,973,262,086)	$ (7,726,797,654)
Ireland 2.5%Batch hedge 2% tax(28%)	$ 4,915,584,022	$ (1,854,849,014)	$ (3,035,819,492)	$ 6,205,183,509	$ (1,531,325,011)	$ (2,783,312,537)	$ (1,289,599,487)	$ (3,745,001,698)	$ (7,309,027,205)
Ireland 2.5%Batch hedge 4% tax(28%)	$ 5,001,824,919	$ (1,815,817,151)	$ (2,974,760,504)	$ 6,150,250,791	$ (1,559,713,409)	$ (2,779,951,841)	$ (1,148,425,872)	$ (3,359,194,531)	$ (6,069,849,275)

Table A3: US/Non US Generic Manufacturing Batch NPV Scenarios

		US Batch Manufacturing			NonUS Batch Manufacturing			US - NonUS Batch Manufacturing	
US Batch wih China Batch	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
China 2.5%Batch hedge 1% tax(21%)	$ 3,688,283,620	$ (4,196,568,440)	$ (5,243,152,824)	$ 3,481,773,160	$ (4,119,662,289)	$ (5,176,964,716)	$ 206,510,460	$ (88,404,526)	$ (95,846,685)
China 2.5%Batch hedge 2% tax(21%)	$ 3,761,198,264	$ (4,169,543,197)	$ (5,261,330,469)	$ 3,489,524,641	$ (4,126,498,433)	$ (5,243,235,527)	$ 271,673,623	$ (65,055,292)	$ (76,255,136)
China 2.5%Batch hedge 4% tax(21%)	$ 3,804,974,944	$ (4,209,513,787)	$ (5,271,162,493)	$ 3,409,094,875	$ (4,259,642,593)	$ (5,355,860,868)	$ 395,880,069	$ (22,578,579)	$ (42,967,507)
China 2.5%Batch hedge 1% tax(28%)	$ 3,304,284,355	$ (4,175,237,748)	$ (5,328,328,759)	$ 3,539,521,695	$ (4,094,402,422)	$ (5,259,496,277)	$ (235,237,340)	$ (629,367,017)	$ (1,204,130,933)
China 2.5%Batch hedge 2% tax(28%)	$ 3,316,338,062	$ (4,176,676,583)	$ (5,181,660,742)	$ 3,491,428,610	$ (4,137,138,430)	$ (5,161,155,800)	$ (175,090,548)	$ (449,242,698)	$ (844,896,633)
China 2.5%Batch hedge 4% tax(28%)	$ 3,392,276,351	$ (4,152,688,546)	$ (5,194,859,239)	$ 3,446,359,458	$ (4,192,246,407)	$ (5,279,447,289)	$ (54,083,108)	$ (91,169,079)	$ (94,445,971)
US Batch wih India Batch									
India 2.5%Batch hedge 1% tax(21%)	$ 3,809,239,099	$ (4,151,915,143)	$ (5,336,924,416)	$ 3,503,273,533	$ (3,797,656,910)	$ (4,992,415,855)	$ 305,965,566	$ (358,069,672)	$ (371,255,473)
India 2.5%Batch hedge 2% tax(21%)	$ 3,679,799,024	$ (4,128,231,056)	$ (5,178,645,298)	$ 3,331,300,175	$ (3,821,086,473)	$ (4,879,946,896)	$ 348,498,848	$ (329,262,682)	$ (346,087,715)
India 2.5%Batch hedge 4% tax(21%)	$ 3,691,960,652	$ (4,192,484,886)	$ (5,308,090,945)	$ 3,227,284,226	$ (3,964,618,343)	$ (5,113,212,548)	$ 464,676,426	$ (279,082,991)	$ (304,933,526)
India 2.5%Batch hedge 1% tax(28%)	$ 3,301,992,268	$ (4,199,510,208)	$ (5,238,207,376)	$ 3,446,523,974	$ (3,849,685,165)	$ (4,895,502,730)	$ (144,531,706)	$ (361,174,074)	$ (373,889,482)
India 2.5%Batch hedge 2% tax(28%)	$ 3,153,493,051	$ (4,163,915,013)	$ (5,299,321,112)	$ 3,247,593,759	$ (3,851,741,897)	$ (5,006,201,285)	$ (94,100,708)	$ (334,676,192)	$ (349,776,614)
India 2.5%Batch hedge 4% tax(28%)	$ 3,362,514,149	$ (4,221,120,306)	$ (5,241,856,787)	$ 3,331,932,240	$ (3,990,464,679)	$ (5,037,706,422)	$ 30,581,909	$ (290,923,103)	$ (311,991,994)
US Batch wih Ireland Batch									
Ireland 2.5%Batch hedge 1% tax(21%)	$ 3,801,263,756	$ (4,175,055,171)	$ (5,233,704,776)	$ 4,533,684,376	$ (3,939,442,003)	$ (5,012,053,223)	$ (732,420,620)	$ (2,121,007,965)	$ (4,113,686,373)
Ireland 2.5%Batch hedge 2% tax(21%)	$ 3,615,777,295	$ (4,206,881,708)	$ (5,271,773,270)	$ 4,263,441,200	$ (4,009,346,837)	$ (5,098,970,354)	$ (647,663,905)	$ (1,840,061,736)	$ (3,387,014,205)
Ireland 2.5%Batch hedge 4% tax(21%)	$ 3,658,345,469	$ (4,164,410,012)	$ (5,280,769,513)	$ 4,173,736,065	$ (4,047,901,065)	$ (5,204,446,881)	$ (515,390,596)	$ (1,397,463,212)	$ (2,615,574,377)
Ireland 2.5%Batch hedge 1% tax(28%)	$ 3,296,988,787	$ (4,217,663,579)	$ (5,320,193,130)	$ 4,472,286,273	$ (3,983,042,296)	$ (5,099,388,260)	$ (1,175,297,485)	$ (3,806,881,946)	$ (7,338,957,136)
Ireland 2.5%Batch hedge 2% tax(28%)	$ 3,269,427,600	$ (4,105,132,369)	$ (5,202,370,425)	$ 4,365,226,760	$ (3,906,679,736)	$ (5,027,264,949)	$ (1,095,799,159)	$ (3,561,286,769)	$ (7,093,279,174)
Ireland 2.5%Batch hedge 4% tax(28%)	$ 3,194,293,527	$ (4,164,996,500)	$ (5,254,700,875)	$ 4,142,913,218	$ (4,043,264,209)	$ (5,186,862,316)	$ (948,619,691)	$ (3,115,565,632)	$ (6,071,975,666)

Table A4: US- China Brand Manufacturing CM and Batch NPV Scenarios

		US Manufacturing			NonUS Manufacturing			US - NonUS Manufacturing	
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
Brand									
China 2.5%CM hedge 1% tax(21%)	$5,965,048,146	$(1,230,337,857)	$(2,280,496,797)	$5,168,408,023	$(1,734,601,403)	$(2,808,853,816)	$ 796,640,123	$ 501,644,727	$ 480,623,696
China 2.5%CM hedge 2% tax(21%)	$5,876,633,386	$(1,222,718,756)	$(2,351,833,919)	$5,020,068,565	$(1,773,547,699)	$(2,912,681,491)	$ 856,564,821	$ 526,622,318	$ 502,836,203
China 2.5%CM hedge 4% tax(21%)	$5,901,375,078	$(1,291,419,275)	$(2,463,475,665)	$4,911,770,036	$(1,903,984,959)	$(3,098,407,264)	$ 989,605,042	$ 577,151,610	$ 540,645,524
China 10%CM hedge 1% tax(21%)	$5,936,831,872	$(1,189,095,795)	$(2,343,946,951)	$5,151,492,062	$(1,645,147,922)	$(2,841,663,035)	$ 785,339,811	$ 356,742,566	$ 230,307,910
China 10%CM hedge 2% tax(21%)	$6,097,532,479	$(1,308,436,198)	$(2,442,490,116)	$5,233,871,046	$(1,836,098,654)	$(2,969,707,607)	$ 863,661,433	$ 389,853,235	$ 261,193,438
China 10%CM hedge 4% tax(21%)	$5,881,615,920	$(1,247,144,581)	$(2,400,905,384)	$4,901,345,508	$(1,848,643,394)	$(2,989,018,381)	$ 980,270,412	$ 445,093,999	$ 300,431,322
China 15%CM hedge 1% tax(21%)	$5,980,733,876	$(1,314,701,513)	$(2,514,415,204)	$5,200,550,793	$(1,800,083,984)	$(2,968,776,639)	$ 780,183,083	$ 197,590,421	$ (44,367,991)
China 15%CM hedge 2% tax(21%)	$6,036,922,801	$(1,262,485,749)	$(2,388,264,351)	$5,187,393,911	$(1,784,300,185)	$(2,879,222,394)	$ 849,528,890	$ 235,700,503	$ (216,543)
China 15%CM hedge 4% tax(21%)	$5,947,995,526	$(1,251,376,264)	$(2,407,735,786)	$4,974,385,596	$(1,806,830,638)	$(2,925,326,254)	$ 973,609,930	$ 287,843,504	$ 49,949,118
China 2.5%CM hedge 1% tax(28%)	$5,441,274,808	$(1,322,692,751)	$(2,425,636,921)	$5,229,698,311	$(1,750,332,956)	$(2,910,205,598)	$ 211,576,497	$(221,797,856)	$ (816,290,387)
China 2.5%CM hedge 2% tax(28%)	$5,515,013,037	$(1,341,347,626)	$(2,475,466,752)	$5,238,363,423	$(1,797,129,608)	$(2,987,014,737)	$ 276,649,614	$ (25,102,383)	$ (442,218,516)
China 2.5%CM hedge 4% tax(28%)	$5,468,693,956	$(1,323,899,538)	$(2,516,504,622)	$5,057,326,827	$(1,837,771,076)	$(3,103,781,910)	$ 411,367,129	$ 355,177,368	$ 348,360,169
China 10%CM hedge 1% tax(28%)	$5,621,954,005	$(1,330,578,451)	$(2,537,263,449)	$5,424,657,116	$(1,737,500,146)	$(2,967,907,877)	$ 197,296,889	$(271,155,568)	$ (883,794,843)
China 10%CM hedge 2% tax(28%)	$5,407,154,266	$(1,318,294,978)	$(2,477,116,572)	$5,135,935,989	$(1,754,586,443)	$(2,958,229,059)	$ 271,218,276	$ (76,013,863)	$ (476,864,903)
China 10%CM hedge 4% tax(28%)	$5,428,553,579	$(1,264,525,044)	$(2,475,685,542)	$5,026,418,353	$(1,768,315,217)	$(3,011,605,007)	$ 402,135,226	$ 182,090,874	$ 78,746,022
China 15%CM hedge 1% tax(28%)	$5,373,664,753	$(1,415,520,019)	$(2,534,005,760)	$5,174,863,426	$(1,778,623,263)	$(2,889,323,408)	$ 198,801,327	$(335,482,053)	$ (861,827,715)
China 15%CM hedge 2% tax(28%)	$5,360,251,434	$(1,383,568,861)	$(2,507,520,549)	$5,100,834,024	$(1,793,338,727)	$(2,944,299,955)	$ 259,417,410	$(208,654,096)	$ (579,428,417)
China 15%CM hedge 4% tax(28%)	$5,469,956,417	$(1,361,367,486)	$(2,458,536,812)	$5,078,991,311	$(1,791,399,055)	$(2,978,070,191)	$ 390,965,106	$ 8,548,480	$ (191,157,844)

Table A5: US-India Brand Manufacturing CM and Batch NPV Scenarios

	US Manufacturing			NonUS Manufacturing			US - NonUS Manufacturing		
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
Brand									
India 2.5%CM hedge 1% tax(21%)	$ 5,941,256,520	$ (1,214,967,977)	$ (2,378,174,428)	$ 4,950,762,049	$ (1,555,541,938)	$ (2,696,409,762)	$ 990,494,471	$ 333,266,664	$ 289,514,281
India 2.5%CM hedge 2% tax(21%)	$ 6,155,536,854	$ (1,338,747,884)	$ (2,500,539,141)	$ 5,072,285,715	$ (1,710,196,204)	$ (2,842,579,364)	$ 1,083,251,138	$ 354,993,906	$ 314,514,586
India 2.5%CM hedge 4% tax(21%)	$ 5,912,573,861	$ (1,250,365,324)	$ (2,355,649,076)	$ 4,736,167,734	$ (1,688,367,469)	$ (2,772,315,090)	$ 1,176,406,127	$ 416,075,622	$ 366,086,760
India 10%CM hedge 1% tax(21%)	$ 5,983,689,227	$ (1,239,363,456)	$ (2,422,456,877)	$ 4,996,040,423	$ (1,577,950,077)	$ (2,714,001,530)	$ 987,648,804	$ 235,180,847	$ 82,160,938
India 10%CM hedge 2% tax(21%)	$ 6,066,693,860	$ (1,248,639,991)	$ (2,422,895,844)	$ 5,000,066,168	$ (1,624,052,891)	$ (2,759,293,488)	$ 1,066,627,691	$ 269,234,523	$ 114,688,665
India 10%CM hedge 4% tax(21%)	$ 6,189,810,263	$ (1,212,053,789)	$ (2,407,221,683)	$ 4,984,319,741	$ (1,640,485,696)	$ (2,767,322,974)	$ 1,205,490,522	$ 319,761,652	$ 152,432,767
India 15%CM hedge 1% tax(21%)	$ 6,043,796,906	$ (1,289,173,399)	$ (2,497,771,210)	$ 5,061,052,473	$ (1,610,664,831)	$ (2,657,500,022)	$ 982,744,433	$ 86,704,309	$ (162,547,443)
India 15%CM hedge 2% tax(21%)	$ 5,841,804,142	$ (1,302,092,257)	$ (2,516,828,545)	$ 4,816,188,725	$ (1,628,966,773)	$ (2,790,753,315)	$ 1,025,615,417	$ 126,046,213	$ (125,203,295)
India 15%CM hedge 4% tax(21%)	$ 6,218,391,254	$ (1,213,499,237)	$ (2,410,133,988)	$ 5,017,799,295	$ (1,631,579,019)	$ (2,659,648,220)	$ 1,200,591,959	$ 181,168,934	$ (73,859,451)
India 2.5%CM hedge 1% tax(28%)	$ 5,337,444,385	$ (1,316,054,958)	$ (2,455,808,611)	$ 4,927,646,814	$ (1,572,577,076)	$ (2,713,572,927)	$ 409,797,571	$ 245,623,384	$ 233,128,434
India 2.5%CM hedge 2% tax(28%)	$ 5,455,567,616	$ (1,311,928,353)	$ (2,377,654,829)	$ 4,978,142,750	$ (1,599,462,945)	$ (2,670,006,625)	$ 477,424,865	$ 269,808,816	$ 251,613,698
India 2.5%CM hedge 4% tax(28%)	$ 5,333,618,609	$ (1,307,562,056)	$ (2,350,760,949)	$ 4,736,563,033	$ (1,658,461,320)	$ (2,723,345,646)	$ 597,055,576	$ 313,950,316	$ 285,196,849
India 10%CM hedge 1% tax(28%)	$ 5,264,701,361	$ (1,363,752,841)	$ (2,519,679,633)	$ 4,866,099,589	$ (1,608,472,914)	$ (2,762,810,053)	$ 398,601,772	$ 76,439,767	$ (36,966,511)
India 10%CM hedge 2% tax(28%)	$ 5,365,106,641	$ (1,314,068,184)	$ (2,445,291,957)	$ 4,896,478,146	$ (1,571,770,570)	$ (2,730,823,570)	$ 468,628,495	$ 113,747,234	$ 6,758,959
India 10%CM hedge 4% tax(28%)	$ 5,406,492,412	$ (1,428,258,017)	$ (2,543,586,087)	$ 4,810,857,757	$ (1,775,527,697)	$ (2,830,153,503)	$ 595,634,655	$ 165,571,050	$ 27,621,269
India 15%CM hedge 1% tax(28%)	$ 5,395,941,118	$ (1,377,769,292)	$ (2,524,758,642)	$ 4,999,063,493	$ (1,593,436,626)	$ (2,747,526,001)	$ 396,877,626	$ (69,100,624)	$ (284,619,235)
India 15%CM hedge 2% tax(28%)	$ 5,467,991,555	$ (1,385,336,522)	$ (2,521,944,282)	$ 5,011,103,683	$ (1,624,056,522)	$ (2,766,378,562)	$ 456,887,872	$ (46,876,737)	$ (275,664,682)
India 15%CM hedge 4% tax(28%)	$ 5,482,721,957	$ (1,391,421,341)	$ (2,629,960,351)	$ 4,894,515,353	$ (1,680,939,023)	$ (2,901,281,346)	$ 588,206,605	$ 19,455,680	$ (228,400,633)

Table A6: US-Ireland Brand Manufacturing CM and Batch NPV Scenarios

		US Manufacturing			NonUS Manufacturing			US - NonUS Manufacturing	
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
Brand									
Ireland 2.5%CM hedge 1% tax(21%)	$6,221,380,485	$(1,255,546,068)	$(2,364,218,269)	$6,553,058,300	$(1,513,715,210)	$(2,682,910,300)	$ (331,677,815)	$(1,711,643,521)	$(3,990,013,145)
Ireland 2.5%CM hedge 2% tax(21%)	$5,791,261,152	$(1,303,148,603)	$(2,375,746,811)	$6,008,018,584	$(1,598,564,618)	$(2,714,519,895)	$ (216,757,433)	$(1,367,198,457)	$(3,027,378,636)
Ireland 2.5%CM hedge 4% tax(21%)	$5,860,053,402	$(1,232,760,321)	$(2,366,883,301)	$5,931,347,183	$(1,593,479,353)	$(2,775,948,515)	$ (71,293,781)	$(1,006,716,282)	$(2,214,055,054)
Ireland 10%CM hedge 1% tax(21%)	$6,083,851,367	$(1,229,884,270)	$(2,475,862,528)	$6,413,992,355	$(1,464,163,262)	$(2,679,408,583)	$ (330,140,988)	$(1,723,153,141)	$(3,641,930,068)
Ireland 10%CM hedge 2% tax(21%)	$5,984,598,020	$(1,246,404,416)	$(2,453,090,467)	$6,227,768,540	$(1,520,477,755)	$(2,747,849,933)	$ (243,170,521)	$(1,462,777,184)	$(3,207,488,474)
Ireland 10%CM hedge 4% tax(21%)	$5,981,086,696	$(1,241,698,340)	$(2,416,194,370)	$6,069,922,274	$(1,580,854,851)	$(2,760,482,979)	$ (88,835,578)	$(1,018,566,720)	$(2,216,448,222)
Ireland 15%CM hedge 1% tax(21%)	$5,987,230,861	$(1,263,058,847)	$(2,433,599,722)	$6,320,669,198	$(1,420,088,588)	$(2,653,450,955)	$ (333,438,337)	$(1,688,091,629)	$(3,727,021,642)
Ireland 15%CM hedge 2% tax(21%)	$6,015,118,158	$(1,247,828,749)	$(2,372,094,139)	$6,272,965,616	$(1,476,603,664)	$(2,667,267,895)	$ (257,847,458)	$(1,543,243,656)	$(3,289,598,362)
Ireland 15%CM hedge 4% tax(21%)	$5,892,179,002	$(1,328,013,803)	$(2,499,347,125)	$5,986,561,253	$(1,629,531,705)	$(2,819,887,214)	$ (94,382,252)	$(1,071,312,330)	$(2,266,788,669)
Ireland 2.5%CM hedge 1% tax(28%)	$5,414,677,401	$(1,333,049,927)	$(2,525,313,300)	$6,313,371,526	$(1,501,522,276)	$(2,801,935,198)	$ (898,694,125)	$(3,509,883,369)	$(7,655,793,886)
Ireland 2.5%CM hedge 2% tax(28%)	$5,405,254,809	$(1,282,049,224)	$(2,418,845,016)	$6,222,657,529	$(1,466,761,474)	$(2,703,357,942)	$ (817,402,720)	$(3,153,612,909)	$(7,112,309,543)
Ireland 2.5%CM hedge 4% tax(28%)	$5,292,732,355	$(1,315,613,814)	$(2,406,858,393)	$5,938,106,869	$(1,592,827,740)	$(2,775,386,125)	$ (645,374,514)	$(2,716,098,806)	$(5,777,895,171)
Ireland 10%CM hedge 1% tax(28%)	$5,277,159,845	$(1,379,118,230)	$(2,619,887,528)	$6,159,277,626	$(1,516,148,498)	$(2,842,794,840)	$ (882,117,781)	$(3,500,257,925)	$(6,902,419,003)
Ireland 10%CM hedge 2% tax(28%)	$5,512,206,443	$(1,416,026,309)	$(2,480,751,031)	$6,361,629,758	$(1,600,197,823)	$(2,752,256,025)	$ (849,423,315)	$(3,412,966,707)	$(7,504,903,456)
Ireland 10%CM hedge 4% tax(28%)	$5,339,269,801	$(1,396,785,911)	$(2,534,192,461)	$6,003,340,612	$(1,623,912,644)	$(2,905,376,038)	$ (664,070,810)	$(2,771,032,410)	$(5,938,628,685)
Ireland 15%CM hedge 1% tax(28%)	$5,272,506,688	$(1,341,663,818)	$(2,418,767,416)	$6,165,992,577	$(1,453,057,392)	$(2,564,268,939)	$ (893,485,890)	$(3,472,455,410)	$(7,207,984,184)
Ireland 15%CM hedge 2% tax(28%)	$5,369,387,215	$(1,398,936,362)	$(2,523,354,762)	$6,206,018,884	$(1,543,496,121)	$(2,668,560,654)	$ (836,631,669)	$(3,301,929,908)	$(6,708,427,372)
Ireland 15%CM hedge 4% tax(28%)	$5,352,420,228	$(1,377,208,768)	$(2,419,459,081)	$6,027,986,445	$(1,619,567,218)	$(2,692,489,538)	$ (675,566,216)	$(2,892,148,349)	$(6,092,637,740)

Table A7: US-China Generic Manufacturing CM and Batch NPV Scenarios

		US Manufacturing		NonUS Manufacturing			US - NonUS Manufacturing	
	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
Generic									
China 2.5%CM hedge 1% tax(21%)	$ 4,413,059,539	$ (3,522,482,606)	$ (4,599,851,519)	$ 3,622,103,893	$ (4,090,075,967)	$ (5,176,463,149)	$ 790,955,646	$ 523,438,910	$ 505,119,284
China 2.5%CM hedge 2% tax(21%)	$ 4,352,473,210	$ (3,585,234,514)	$ (4,697,810,318)	$ 3,503,240,400	$ (4,201,942,448)	$ (5,331,785,843)	$ 849,232,809	$ 542,133,535	$ 519,334,316
China 2.5%CM hedge 4% tax(21%)	$ 4,214,040,839	$ (3,579,587,393)	$ (4,670,084,397)	$ 3,253,211,124	$ (4,274,955,928)	$ (5,412,393,369)	$ 960,829,716	$ 578,145,922	$ 550,284,745
China 10%CM hedge 1% tax(21%)	$ 4,134,965,679	$ (3,497,173,436)	$ (4,707,649,506)	$ 3,370,807,665	$ (4,052,558,467)	$ (5,206,166,696)	$ 764,158,014	$ 324,940,220	$ 190,676,470
China 10%CM hedge 2% tax(21%)	$ 4,371,078,135	$ (3,516,813,999)	$ (4,692,080,162)	$ 3,531,300,806	$ (4,107,914,797)	$ (5,282,384,320)	$ 839,777,329	$ 352,384,460	$ 205,599,369
China 10%CM hedge 4% tax(21%)	$ 4,337,854,997	$ (3,591,425,391)	$ (4,669,652,812)	$ 3,378,800,976	$ (4,271,938,328)	$ (5,346,209,361)	$ 959,054,022	$ 408,567,236	$ 252,946,909
China 15%CM hedge 1% tax(21%)	$ 4,313,227,074	$ (3,536,508,910)	$ (4,637,205,602)	$ 3,551,281,248	$ (4,019,818,017)	$ (5,154,195,029)	$ 761,945,825	$ 154,943,497	$ (103,914,503)
China 15%CM hedge 2% tax(21%)	$ 4,297,742,370	$ (3,526,117,060)	$ (4,752,295,147)	$ 3,476,594,789	$ (4,099,754,793)	$ (5,274,565,252)	$ 821,147,581	$ 156,674,110	$ (87,974,387)
China 15%CM hedge 4% tax(21%)	$ 4,285,616,122	$ (3,519,199,092)	$ (4,652,023,152)	$ 3,345,835,771	$ (4,159,991,484)	$ (5,250,059,242)	$ 939,780,351	$ 217,202,493	$ (19,954,595)
China 2.5%CM hedge 1% tax(28%)	$ 3,823,170,622	$ (3,499,219,173)	$ (4,627,418,185)	$ 3,505,925,441	$ (4,067,860,415)	$ (5,217,327,033)	$ 317,245,182	$ (135,400,059)	$ (657,109,072)
China 2.5%CM hedge 2% tax(28%)	$ 3,898,785,988	$ (3,460,204,773)	$ (4,626,706,892)	$ 3,523,542,345	$ (4,065,122,825)	$ (5,259,190,616)	$ 375,243,642	$ 37,060,969	$ (330,230,667)
China 2.5%CM hedge 4% tax(28%)	$ 3,868,789,137	$ (3,520,993,868)	$ (4,644,192,993)	$ 3,371,566,950	$ (4,210,571,601)	$ (5,375,081,525)	$ 497,222,186	$ 378,758,430	$ 367,692,593
China 10%CM hedge 1% tax(28%)	$ 3,718,512,496	$ (3,614,502,635)	$ (4,653,594,510)	$ 3,408,354,018	$ (4,113,786,396)	$ (5,183,299,221)	$ 310,158,477	$ (178,339,252)	$ (699,888,506)
China 10%CM hedge 2% tax(28%)	$ 3,951,438,276	$ (3,559,479,505)	$ (4,681,884,178)	$ 3,587,098,157	$ (4,146,558,737)	$ (5,246,893,570)	$ 364,340,119	$ (40,753,238)	$ (381,324,285)
China 10%CM hedge 4% tax(28%)	$ 3,667,291,655	$ (3,579,932,980)	$ (4,670,954,998)	$ 3,182,200,596	$ (4,243,959,567)	$ (5,385,415,987)	$ 485,091,060	$ 207,432,818	$ 85,685,950
China 15%CM hedge 1% tax(28%)	$ 3,622,852,335	$ (3,610,897,008)	$ (4,898,328,689)	$ 3,324,575,159	$ (4,106,338,172)	$ (5,326,945,237)	$ 298,277,177	$ (285,089,110)	$ (798,388,929)
China 15%CM hedge 2% tax(28%)	$ 3,811,118,239	$ (3,663,005,582)	$ (4,830,027,465)	$ 3,459,204,175	$ (4,208,750,939)	$ (5,351,411,351)	$ 351,914,065	$ (179,993,297)	$ (525,507,353)
China 15%CM hedge 4% tax(28%)	$ 3,657,427,671	$ (3,695,138,613)	$ (4,849,546,717)	$ 3,181,854,003	$ (4,294,907,686)	$ (5,465,463,027)	$ 475,573,668	$ 39,249,975	$ (204,073,696)

Table A8: US-India Generic Manufacturing CM and Batch NPV Scenarios

		US CM Manufacturing			Non US Batch Manufacturing			US - Non US Manufacturing	
Generic	Expected NPV	95th Percentile	99 percentile	Expected NPV	95th Percentile	99 percentile	Expected NPV	95th Percentile	99 percentile
India 2.5%CM hedge 1% tax(21%)	$ 4,237,541,934	$ (3,482,589,169)	$ (4,663,051,187)	$ 3,369,719,106	$ (3,782,667,282)	$ (4,967,419,690)	$ 867,822,827	$ 282,955,830	$ 270,594,765
India 2.5%CM hedge 2% tax(21%)	$ 4,250,446,578	$ (3,554,593,598)	$ (4,630,286,571)	$ 3,323,871,004	$ (3,891,854,428)	$ (4,984,268,547)	$ 926,575,574	$ 307,432,730	$ 290,337,598
India 2.5%CM hedge 4% tax(21%)	$ 4,312,611,029	$ (3,517,276,513)	$ (4,639,218,607)	$ 3,265,099,253	$ (3,935,895,396)	$ (5,095,472,238)	$ 1,047,511,777	$ 349,091,554	$ 325,540,045
India 10%CM hedge 1% tax(21%)	$ 4,345,982,828	$ (3,583,105,788)	$ (4,682,381,970)	$ 3,471,004,918	$ (3,854,757,163)	$ (4,929,418,461)	$ 874,977,910	$ 110,037,840	$ (44,621,797)
India 10%CM hedge 2% tax(21%)	$ 4,303,503,095	$ (3,537,209,127)	$ (4,586,530,135)	$ 3,382,639,960	$ (3,871,391,496)	$ (4,946,464,481)	$ 920,863,135	$ 131,136,780	$ (27,445,990)
India 10%CM hedge 4% tax(21%)	$ 4,297,641,666	$ (3,605,894,987)	$ (4,686,444,707)	$ 3,260,413,709	$ (3,978,356,394)	$ (5,123,838,693)	$ 1,037,227,957	$ 179,864,250	$ 19,404,130
India 15%CM hedge 1% tax(21%)	$ 4,281,825,947	$ (3,561,680,602)	$ (4,768,126,821)	$ 3,437,406,732	$ (3,796,573,734)	$ (4,940,378,426)	$ 844,419,215	$ (75,864,972)	$ (367,753,478)
India 15%CM hedge 2% tax(21%)	$ 4,350,045,033	$ (3,546,270,368)	$ (4,636,268,812)	$ 3,434,722,025	$ (3,855,846,506)	$ (4,929,153,588)	$ 915,323,008	$ (23,663,342)	$ (314,287,549)
India 15%CM hedge 4% tax(21%)	$ 4,400,121,831	$ (3,544,999,838)	$ (4,667,549,308)	$ 3,365,584,557	$ (3,912,318,514)	$ (4,961,418,281)	$ 1,034,537,273	$ 2,635,156	$ (270,755,911)
India 2.5%CM hedge 1% tax(28%)	$ 3,752,208,079	$ (3,491,286,479)	$ (4,623,255,283)	$ 3,348,987,074	$ (3,784,465,223)	$ (4,925,587,225)	$ 403,221,005	$ 255,260,162	$ 241,335,172
India 2.5%CM hedge 2% tax(28%)	$ 3,813,980,922	$ (3,561,765,176)	$ (4,648,069,895)	$ 3,351,572,988	$ (3,892,869,763)	$ (5,006,426,141)	$ 462,407,934	$ 273,260,131	$ 256,895,377
India 2.5%CM hedge 4% tax(28%)	$ 3,809,292,010	$ (3,446,532,846)	$ (4,527,050,808)	$ 3,235,608,126	$ (3,852,329,734)	$ (4,974,065,965)	$ 573,683,884	$ 305,063,067	$ 281,285,554
India 10%CM hedge 1% tax(28%)	$ 3,636,426,742	$ (3,582,676,769)	$ (4,657,988,527)	$ 3,247,349,353	$ (3,838,690,215)	$ (4,935,155,321)	$ 389,077,389	$ 39,239,800	$ (110,982,240)
India 10%CM hedge 2% tax(28%)	$ 3,867,490,764	$ (3,584,297,000)	$ (4,750,910,182)	$ 3,412,880,607	$ (3,885,467,893)	$ (5,068,035,101)	$ 454,610,156	$ 76,446,866	$ (76,508,398)
India 10%CM hedge 4% tax(28%)	$ 3,788,701,536	$ (3,441,574,517)	$ (4,598,535,786)	$ 3,225,472,608	$ (3,809,400,710)	$ (4,973,356,466)	$ 563,228,929	$ 128,963,398	$ (1,226,655)
India 15%CM hedge 1% tax(28%)	$ 3,865,633,526	$ (3,552,167,068)	$ (4,745,243,931)	$ 3,479,150,098	$ (3,816,222,661)	$ (4,939,002,591)	$ 386,483,428	$ (138,033,323)	$ (390,314,738)
India 15%CM hedge 2% tax(28%)	$ 3,754,251,110	$ (3,558,502,891)	$ (4,769,460,783)	$ 3,315,408,944	$ (3,828,877,019)	$ (4,988,386,455)	$ 438,842,166	$ (106,198,876)	$ (361,992,328)
India 15%CM hedge 4% tax(28%)	$ 3,730,174,982	$ (3,648,179,010)	$ (4,747,045,153)	$ 3,180,620,204	$ (3,970,790,911)	$ (5,066,342,696)	$ 549,554,778	$ (72,028,782)	$ (339,105,143)

Table A9: US-Ireland Generic Manufacturing CM and Batch NPV Scenarios

		US CM Manufacturing			Non US Batch Manufacturing			US - Non US Manufacturing	
Generic	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile	Expected NPV	95th Percentile	99th Percentile
Ireland 2.5%CM hedge 1% tax(21%)	$ 4,267,045,320	$ (3,569,721,201)	$ (4,696,733,996)	$ 4,412,489,361	$ (3,983,722,162)	$ (5,122,675,690)	$ (145,444,040)	$ (1,522,735,325)	$ (3,322,565,272)
Ireland 2.5%CM hedge 2% tax(21%)	$ 4,401,071,328	$ (3,472,530,007)	$ (4,607,458,968)	$ 4,489,423,316	$ (3,917,086,062)	$ (5,089,021,112)	$ (88,351,988)	$ (1,392,085,922)	$ (3,029,855,192)
Ireland 2.5%CM hedge 4% tax(21%)	$ 4,332,734,511	$ (3,555,632,301)	$ (4,672,579,535)	$ 4,277,834,668	$ (4,083,037,900)	$ (5,247,092,058)	$ 54,899,843	$ (944,197,671)	$ (2,192,337,859)
Ireland 10%CM hedge 1% tax(21%)	$ 4,260,719,780	$ (3,581,854,826)	$ (4,703,632,080)	$ 4,416,109,114	$ (3,955,493,122)	$ (5,031,201,014)	$ (155,389,334)	$ (1,503,188,506)	$ (3,453,282,517)
Ireland 10%CM hedge 2% tax(21%)	$ 4,357,169,047	$ (3,553,775,489)	$ (4,671,741,593)	$ 4,450,292,514	$ (3,982,354,645)	$ (5,086,257,760)	$ (93,123,467)	$ (1,405,610,225)	$ (2,897,815,214)
Ireland 10%CM hedge 4% tax(21%)	$ 4,191,290,229	$ (3,535,988,305)	$ (4,649,526,183)	$ 4,140,082,950	$ (4,064,843,048)	$ (5,186,256,488)	$ 51,207,279	$ (915,931,025)	$ (2,148,542,587)
Ireland 15%CM hedge 1% tax(21%)	$ 4,282,082,659	$ (3,601,291,231)	$ (4,707,230,690)	$ 4,458,479,179	$ (3,925,257,631)	$ (5,013,420,836)	$ (176,396,519)	$ (1,629,019,907)	$ (3,686,617,572)
Ireland 15%CM hedge 2% tax(21%)	$ 4,190,349,410	$ (3,562,746,356)	$ (4,729,342,205)	$ 4,288,790,795	$ (3,944,861,261)	$ (5,090,004,481)	$ (98,441,385)	$ (1,400,605,347)	$ (2,903,205,337)
Ireland 15%CM hedge 4% tax(21%)	$ 4,270,957,920	$ (3,612,038,174)	$ (4,602,365,340)	$ 4,237,149,972	$ (4,064,523,743)	$ (5,066,331,726)	$ 33,807,948	$ (974,595,293)	$ (2,224,433,669)
Ireland 2.5%CM hedge 1% tax(28%)	$ 3,883,525,587	$ (3,531,357,790)	$ (4,694,353,498)	$ 4,509,991,019	$ (3,943,252,943)	$ (5,132,993,078)	$ (626,465,432)	$ (3,322,063,207)	$ (6,893,208,209)
Ireland 2.5%CM hedge 2% tax(28%)	$ 3,831,412,880	$ (3,586,098,235)	$ (4,681,418,581)	$ 4,380,998,350	$ (4,033,996,026)	$ (5,153,650,171)	$ (549,585,470)	$ (3,101,484,516)	$ (6,064,687,297)
Ireland 2.5%CM hedge 4% tax(28%)	$ 3,754,722,557	$ (3,497,400,029)	$ (4,650,070,994)	$ 4,152,933,206	$ (4,018,397,179)	$ (5,217,621,695)	$ (398,210,648)	$ (2,581,181,233)	$ (5,598,271,991)
Ireland 10%CM hedge 1% tax(28%)	$ 3,797,686,285	$ (3,580,191,493)	$ (4,731,683,631)	$ 4,421,597,649	$ (3,952,058,487)	$ (5,121,581,006)	$ (623,911,364)	$ (3,207,195,087)	$ (6,784,855,054)
Ireland 10%CM hedge 2% tax(28%)	$ 3,708,525,917	$ (3,560,393,279)	$ (4,646,689,253)	$ 4,243,033,935	$ (3,999,090,359)	$ (5,075,881,165)	$ (534,508,018)	$ (3,018,214,209)	$ (6,454,062,337)
Ireland 10%CM hedge 4% tax(28%)	$ 3,857,153,917	$ (3,543,613,848)	$ (4,704,272,891)	$ 4,287,719,470	$ (3,987,909,915)	$ (5,253,482,018)	$ (430,565,553)	$ (2,725,168,902)	$ (5,582,001,831)
Ireland 15%CM hedge 1% tax(28%)	$ 3,791,370,004	$ (3,573,026,252)	$ (4,788,134,622)	$ 4,422,726,693	$ (3,996,037,156)	$ (5,106,968,264)	$ (631,356,689)	$ (3,293,829,739)	$ (6,678,919,389)
Ireland 15%CM hedge 2% tax(28%)	$ 3,895,130,454	$ (3,537,785,950)	$ (4,801,315,976)	$ 4,483,194,886	$ (3,896,330,804)	$ (5,113,000,634)	$ (588,064,432)	$ (3,264,221,478)	$ (6,531,165,655)
Ireland 15%CM hedge 4% tax(28%)	$ 3,841,155,104	$ (3,615,334,540)	$ (4,729,434,941)	$ 4,283,596,901	$ (4,069,440,630)	$ (5,186,977,406)	$ (442,441,797)	$ (2,775,487,952)	$ (5,706,872,383)