MAKING DO IN MAKING DRUGS: INNOVATION POLICY AND PHARMACEUTICAL MANUFACTURING

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ABSTRACT

Drug recalls, contamination events, and shortages are on the rise, but drug companies still rely on decades-old manufacturing plants and processes. Contrary to widespread perceptions, drug manufacturing is typically expensive, inefficient, and non-innovative. Drug companies spend much more on manufacturing than on research and development, but the industry lags far behind the innovative manufacturing found in other industries. This lack of innovation in drug manufacturing stands in stark contrast to the innovation present in drug discovery. Drug discovery is the focus of a calibrated innovation policy that combines patents and the regulatory regime. Manufacturing lacks such attention, and the costs are great, both in dollars and in human lives. This article addresses the previously underappreciated role of manufacturing in innovation studies and policy.

The stagnation of pharmaceutical manufacturing results from regulatory barriers and ineffective intellectual-property incentives. As a result of the difficulty enforcing manufacturing process patents, manufacturers tend to rely on trade secrecy instead, which reduces innovation. Making matters worse, regulation actively impedes innovative changes to manufacturing methods through substantive and procedural barriers across the lifespan of a drug. To address these challenges, this article suggests several direct regulatory reforms. It also proposes novel ways that regulation can be used to change the function of intellectual property incentives, which fit particularly well in the drug manufacturing context but could be extended to different areas of innovation policy. For example, FDA could be charged with operating a system of temporary market exclusivity for manufacturing innovation parallel to the patent

system. Alternately, FDA could require disclosure of manufacturing methods to drive the industry from opacity and trade secrecy towards transparency and patent protection for innovation. A better targeted and more effective innovation policy could improve the current sad state of drug manufacturing with potentially immense economic and health benefits.

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INTRODUCTION

M&M chocolate candies are made with a precision far beyond the capabilities of many drug manufacturers.\(^1\) This disparity is surprising; the drug industry is tightly regulated by the U.S. Food and Drug Administration, which also regulates food production, and the quality of drugs has major implications for human health. Nevertheless, drug manufacturing is expensive, inefficient, and non-innovative, which leads to major problems for the healthcare system and society as a whole.

Drug recalls based on quality problems are one such problem. Overall, a record 2,329 drug products were recalled in 2011, the vast majority because of quality problems or contamination during manufacturing or repackaging.\(^2\) In 2009, two drug manufacturers recalled contaminated batches of the crucial anesthetic drug propofol, which led to long-lasting shortages of the drug and one manufacturer’s exit from the market.\(^3\) In early 2012, Novartis recalled Excedrin and other popular over-the-counter pills because some pill bottles contained powerful opiates and broken tablets in addition to their intended contents;\(^4\) the drugs took seven months to return to shelves.\(^5\) And in 2012 and 2013, fungal contamination of steroid injections made by the New England Compounding Center resulted in 48 deaths from fungal meningitis\(^6\) and hundreds of additional infections across 20 states.\(^7\)

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5 Jie Jenny Zou, Excedrin Production Resumes, WSJ BLOGS - HEALTH BLOG (2012).


Drug manufacturing problems are broader than recalls and contamination. In a time of soaring healthcare costs, with over 15% spent on drugs, up to $50 billion annually in wasted dollars is attributable to inefficient drug manufacturing. Overall, manufacturing costs comprise from 15% to over 50% of firm-level revenues. Reducing manufacturing expenses would create tremendous positive social externalities, whether the savings were passed on to consumers (and the government) through lower drug prices or re-invested into research and development (R&D) to increase future health gains. A 20% reduction could create consumer surplus of between $47.4 billion and $574 billion annually, depending on how the saved expenses were used. Despite these potential benefits, firms frequently use outdated production techniques and old manufacturing plants, with little innovative change to increase efficiency or quality.

This lack of innovation is striking within an industry which is otherwise a major and successful focus of innovation policy. Intellectual property and regulatory barriers administered by the United States Food and Drug Administration (FDA) create carefully calibrated incentives for firms to discover and develop drugs. In addition to their independent effects, the two work together: regulation not only creates hurdles to overcome but also enhances patent incentives.

The effect of innovation policy on drug discovery and development has been well studied. But policy and academic debates about innovation
incentives have largely ignored the important role of manufacturing innovation. One of the goals of this article is to secure a place for manufacturing in innovation theory. Manufacturing is important but usually unproblematic. Innovative products require successful manufacture and distribution to create significant social welfare gains. In most industries, firms have sufficient incentives, and face sufficiently low hurdles to innovative manufacturing, that they have improved manufacturing and can reliably provide marketable products. Yet in the pharmaceutical industry, manufacturing has suffered from innovation policy myopia. Patent law does not reward manufacturing innovation, and FDA regulations impede it—so firms tend not to innovate. If manufacturing is better understood in innovation theory, policy prescriptions can use that theory to improve innovation in manufacturing in general and in the pharmaceutical industry in particular.

Incentives are much weaker for innovative manufacturing than for innovative drug discovery. Both patents and FDA action create periods of market exclusivity for new drugs; in addition, the FDA approval process itself strengthens the market power of drug patents. Patents on manufacturing processes, on the other hand, are very hard to enforce, and get no boost from FDA. Firms therefore forego manufacturing patents for trade secrets, which block cumulative innovation and may insufficiently reward some important types of manufacturing innovation. Other industries may also face inadequate incentives for manufacturing innovation, but do not face the intense regulatory barriers present in the pharmaceutical industry.

That regulation also slows manufacturing innovation. Rather than enhancing and fine-tuning innovation incentives, FDA regulation obstructs manufacturing innovation by raising significant barriers to innovative change, both before and after drug approval. Firms avoid introducing new technologies when seeking approval based on historically justified fears of pre-approval delay from reviewers leery of new technology. After approval is gained, changes to manufacturing processes face procedural hurdles which can wholly prevent continual process improvement. Substantive barriers also arise from regulatory lock-in of both drug characteristics and associated manufacturing methods at an early stage in drug development, before firms optimize manufacturing. Pervading the innovative landscape is one final barrier: a form of self-imposed technological standard created

by industry-wide adherence to technical examples in FDA guidance documents.

Broader than any specific failure of innovation or regulation is the mismatch between the two. In the classic justification for intellectual property, socially suboptimal investment in innovation, with an assumed background of regulatory freedom to innovate, is remedied by intellectual property protection which increases innovation incentives. When intellectual property incentives are less effective but innovation is unhampered by regulation, as is the case with manufacturing methods in many industries, firms still innovate to some degree, driven by other competitive incentives. And when regulatory restrictions are intense and costly, but policy rewards are high—as with the development of new drugs, which require costly clinical trials but receive effective patent protection and regulatory market exclusivity—firms still innovate because the benefits of innovation exceed the costs. But when, as with drug manufacturing, regulatory burdens to innovation are major and exclusivity incentives are weak and ineffective, the net motivation to innovate is low.

In the face of this ineffective innovation policy, drug manufacturing has been close to stagnant for decades, lagging far behind the innovative manufacturing advances of other industries. Even those regulatory standards now imposed reflect a relatively poorly controlled state of manufacturing; for instance, the amount of active ingredient in a drug can typically vary by as much as +/− 10%; the difference between two approved tablets in the same bottle could thus be as much as 20%.14

There is no simple complete solution to these problems. Given the broad mismatch between regulatory hurdles and incentives, solutions could lessen hurdles, increase incentives, or do both. The relatively straightforward first step would thus lessen current regulatory barriers to innovation to the extent possible while letting FDA ensure drug safety. This will itself allow more innovation, but is unlikely to be enough, in part because even efficient and well-functioning regulatory oversight imposes significant hurdles in the heavily-regulated drug industry.

More dramatically, FDA can deliberately shape innovation incentives. The effect of regulation on innovation has been studied before,15 but much less attention has been paid to the way regulation can be

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15 This literature is especially extensive in the area of environmental regulation. See, e.g., Jens Hemmelskamp, Environmental Policy Instruments and Their Effects on Innovation, 5 EUR. PLAN. STUD. 177 (1997); Wesley A. Magat, The Effects of Environmental Regulation on Innovation, 43 L. & CONTEMP. PROBS. 4 (1979); Richard B. Stewart, Regulation, Innovation, and Administrative Law: A Conceptual Framework, 69
used as a policy lever to actively drive innovation by changing incentives. FDA administers incentives for drug discovery and development already, but this incentive-shaping approach can be expanded and more flexibly applied to manufacturing innovation in multiple ways. This article suggests two such potential approaches. A system of FDA-mediated market exclusivity could be instituted, parallel to that for drug approval. Alternatively, FDA could mandate disclosure to drive the industry towards far greater transparency about manufacturing methods, destroying the effectiveness of trade secrecy but replacing it with a newly enhanced ability to enforce manufacturing process patents.

Part I of this article evaluates the state of the pharmaceutical manufacturing industry, describing the costs of making drugs, failures of innovation, and potential benefits of increased innovation. Part II describes the regulatory and intellectual property reasons for manufacturing stagnation. Part III suggests potential regulatory solutions to increase innovation, including both pure regulatory and incentive-shifting possibilities.

I. THE STATE OF PHARMACEUTICAL MANUFACTURING

Manufacturing is either the largest or second largest expense for pharmaceutical firms. Nonetheless, drug manufacturing is surprisingly inefficient, lagging significantly behind the modernized manufacturing techniques of other industries; the industry was recently characterized as being “in the dark ages with respect to . . . efficiency.” This manufacturing lag is a major problem: the drug industry could save tens of billions of dollars annually by modernizing manufacturing, with even larger social welfare benefits.

A. High costs

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16 In the context of FDA and drug discovery, see, e.g., Eisenberg, The Role of the FDA in Innovation Policy, supra note 12; W. E. Ridgway, Realizing Two-Tiered Innovation Policy Through Drug Regulation, 58 STAN. L. REV. 1221 (2005).

17 Eisenberg, The Role of the FDA in Innovation Policy, supra note 12.

18 For brand-name and biologics companies, sales and marketing are generally the highest costs; for generics, manufacturing is by far the largest cost. See infra Section I.A.

Widespread perceptions that drug manufacturing is very inexpensive\(^{20}\) arise from a focus on marginal costs, which are in fact frequently very low, especially for blockbuster small-molecule drugs.\(^ {21}\) However, other drugs typically have higher marginal costs, and the industry has very high fixed costs, including building factories, maintaining quality control, and depreciating capital assets. These more inclusive expenses, reported as Cost of Goods Sold (COGS) as a percentage of total revenue, comprise a large fraction of pharmaceutical company costs.

Manufacturing costs differ across different industry segments: brand-name production of small-molecule drugs, generic production of small-molecule drugs, and primarily brand-name production of biologics. For research-oriented brand-name pharmaceutical firms (including “Big Pharma”), COGS were approximately 26% of sales between 1994 and 2006.\(^ {22}\) Generics spend more on manufacturing, averaging 52%.\(^ {23}\) This


\(^{21}\) Marginal costs measure the cost of manufacturing one extra pill; say, going from the one-millionth pill to the one-million-and-first pill. Fixed and marginal production costs vary by drug, and precise production costs are generally unavailable. E. R. Berndt et al., *Information, Marketing, and Pricing in the US Antulcer Drug Market*, THE AMERICAN ECONOMIC REVIEW 100, 100 (1995). Informal discussions with industry officers suggested that for one group of anti-ulcer drugs, marginal production costs ranged from 10-25% of the drugs’ price. *Id*. See also Outterson, *supra* note 13, at 253 (“While the public does not know the true marginal manufacturing costs of most patented drugs, differential pricing and generic production provide useful proxies. Differential pricing ratios currently exceed 30:1 in [anti-retroviral] drugs, implying marginal costs of production in the range of 3 to 4%.”).


\(^{23}\) Basu et al., *supra* note 22, at 33 fig. 1. See also Teva 2011 Annual Report at 6, available at http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-reportsAnnual (last visited January 18, 2013) (Reporting COGS as 48% of sales in 2011 and similar levels in
number is higher for several reasons, including lower prices\textsuperscript{24} and lower R&D, compliance, and marketing costs.\textsuperscript{25} Although it is not \textit{a priori} obvious that absolute (as opposed to fractional) manufacturing costs should be lower for generic companies,\textsuperscript{26} and although hard numbers are difficult to obtain, industry experts suggest that generics also have lower per-unit costs.\textsuperscript{27}

Biologics\textsuperscript{28} also face high manufacturing costs. The manufacture of biologics has been accordingly characterized as “highly complex and requiring high capital investments.”\textsuperscript{29} Both fixed and variable manufacturing costs are higher for biologics than for small molecule drugs.\textsuperscript{30} Fractional manufacturing costs are lower, at 14% of total sales,\textsuperscript{31}

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\textsuperscript{24} Lower prices mean that if absolute manufacturing costs are the same, COGS as a fraction of total sales will be higher. For instance, if it costs $1 to make a pill that sells for $10 as a brand-name pill but $2 as a generic pill, COGS would be 50% of total sales for the generic but only 10% for the brand.

\textsuperscript{25} Basu et al., \textit{supra} note 22, at 33–34.

\textsuperscript{26} Brand-name manufacturers could potentially optimize the manufacturing process over years of experience with the drug. \textit{See} Christopher S. Ponder, \textit{The Dubious Value of Hatch-Waxman Exclusivity}, 45 HOUS. L. REV. 555, 575 (2008) (“In the generic market, the pioneer manufacturer likely enjoys lower manufacturing costs due to valuable experience gained from producing the drug for the duration of its patent.”) Empirically, however, incremental innovation tends not to occur and older techniques persist instead. \textit{See infra} Sections I.B; see also Prabir Basu, \textit{Today’s Hidden Crisis in Health Care: The State of Pharmaceutical Manufacturing}, 3 RPM REPORT (2008), available at http://www.nipte.org/docs/RPM_REPORT.pdf (“The interplay of tight FDA regulation to ensure product safety, the high cost of re-approval of process innovations and inadequate science-based understanding of pharmaceutical science and manufacturing ensures that once a manufacturing process is approved, it is left substantially unchanged for the duration of the product life.”).

\textsuperscript{27} \textit{See} Mark Herlant, \textit{Restoring the Balance: A Strategic Role for Operations, The Pathway to Operational Excellence in the Pharmaceutical Industry} 64, 68 (2010) (“To date, no research-based ‘big pharma’ company has been able to build a COGS model that would allow it to compete in the generics arena.”).

\textsuperscript{28} Biologics include therapeutic proteins and other products of living sources, 42 U.S.C. § 262(i)(1), including major drugs like Avastin and Humira.

\textsuperscript{29} \textit{THOMAS FRIEDLI ET AL., OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY} 153 (Thomas Friedli, 2006) (hereinafter \textit{OPERATIONAL EXCELLENCE}). Biologics can be modified in various and sometimes unpredictable ways during their synthesis; they can vary across production systems or batches, and even within the course of a single production batch. Michael Butler, \textit{Animal Cell Cultures: Recent Achievements and Perspectives in the Production of Biopharmaceuticals}, 68 APPL. MICROBIOL. & BIOTECH. 283, 286–88 (2005); Paradise, \textit{supra} note 7, at 502–03.

\textsuperscript{30} In 2006, an average plant for biologic production was estimated to cost $250-450 million. Henry Grabowski et al., \textit{The Market For Follow-On Biologics: How Will It Evolve?}, 25 HEALTH AFF. 1291, 1294 (2006) By contrast, an average plant for small molecule drug production can be built for $41 million. ED SILVERMAN, \textit{Pharma Closed

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because biologics companies spend significantly more on R&D than small-molecule companies and because the prices for biologics are generally very high, leading to higher fractional operating income. However, despite the fact that manufacturing comprises a smaller portion of revenues for biologics, it remains a significant factor in the dynamics of market entry and market maintenance for biologics.

Overall, drug manufacturing makes up a very large portion of industry expenses across different types of pharmaceutical firms. Despite the size of manufacturing costs, manufacturing is inefficient and non-innovative, which helps drive costs even higher.

B. Lack of innovation

Pharmaceutical manufacturing has lagged far behind other industries in adopting modern manufacturing techniques. These modern techniques, including continuous improvement of processes, quality management throughout production, constant monitoring of production parameters, and waste reduction, were developed principally beginning in the 1980’s and spread through automotive, consumer goods, and other industries, but generally not the drug industry. This lag has resulted in overall poor operational performance in manufacturing, characterized by specific related deficiencies including excessive process rigidity, old plants and equipment, slow development and adoption of novel technology, underutilized equipment and inefficient procedures, a lack of continuous


31 Basu et al., supra note 22, at 33 fig. 1.

32 See Id. at 34 figs 3 and 4 (R&D comprised 26% of total sales for biologics companies versus 13% and 8% for brand-name and generic small molecule drug companies, respectively; operating income was 22%, 19%, and 12% of total sales for biologics, brand-name, and generics, respectively.).

33 FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 24.

34 Id. at 30–33.

35 Id. at 24–25. See also Lawrence Yu, Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control, 25 PHARMACEUTICAL RESEARCH 781, 786 (2008) (noting in 2008 that pharmaceutical development scientists had “just begun” using process simulation to support manufacturing optimization and product development, when that approach had been “successfully used in the chemical and oil industries since the early 1960s.”).

36 See Herlant, supra note 27, at 67 (noting very large gaps between pharmaceutical company performance and “best in class” performance on cycle times, stock turn, and equipment use, and smaller gaps with respect to time in full and reworking products).
A defining characteristic of pharmaceutical manufacturing is process rigidity, where manufacturing parameters remain static over the lifetime of the drug, 38 as opposed to other industries where flexibility and continuous improvement are crucial for efficient and innovative manufacturing. 39 FDA oversight contributes to this process rigidity. 40 Regulations require that formulations and manufacturing techniques used in mass production reproduce the processes used in clinical trials, since those trials were the foundation of FDA’s initial determinations that the approved drugs are safe and effective. 41 However, regulatory submissions on drug characteristics are typically based on relatively limited and shallow information. 42 Thus, the manufacturing conditions described in the initial submission become somewhat arbitrary regulatory commitments which must be kept in future manufacturing. 43

Process rigidity encourages the continued use of outdated production lines and older equipment. Many facilities and primary production lines are quite old; some have been operating continually since the 1960s, frequently running 24 hours a day, 7 days a week, with only limited upgrades. 44 Those facilities increase the risk of contamination of sterile products, require “repeated or extensive manual interventions,” which themselves further increase the contamination risk, and can sometimes even shed glass or metal shavings into the product. 45 The industry’s factories have been generally described as “in terrible shape.” 46 An FDA Warning Letter issued to Ben Venue Labs after a plant inspection on May 2, 2011 described a plant with “severely dented” doors shedding rust into drug containers, rusty tools used for sterile line setup, and a roof

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38 FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 32.
39 Id. at 48 See also THOMAS FRIEDLI ET AL., THE PATHWAY TO OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY 29 (2010) (Pharmaceutical industry lags on continuous improvement.).
40 See infra Section II.A.
41 FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 32.
42 Id. at 25.
43 Id.
45 Id.
46 Katie Thomas, Drug Makers Stalled in a Cycle of Quality Lapses and Shortages, N.Y. TIMES (2012) (quoting Erin Fox, manager of the Drug Information Service at the University of Utah).
leak water into sterile areas.\footnote{47}

These factors—process rigidity and old plants and processes—reflect a broader trend of slow development and adoption of novel technologies. The industry spends little on developing new manufacturing technologies, and is slow to adopt them once developed.\footnote{48} As one example, the sort of academic-industry collaborations which have become common both in drug discovery and in other industries’ manufacturing sectors are just starting to emerge for pharmaceutical manufacturing.\footnote{49} One clear sign of technological lag is that the industry still produces drugs step-by-step in large batches as opposed to the continuous manufacturing—i.e., something like a start-to-finish production line, always moving forward—as is used by almost every other industry.\footnote{50}

In addition to technological slowness, industry manufacturing procedures are plagued by inefficiency. This inefficiency appears in the utilization of capital resources,\footnote{51} management of finished product inventories\footnote{52} and raw material stocks,\footnote{53} and labor practices.\footnote{54}


\footnote{48} See infra Section II.A.1.


\footnote{50} The two major academic-industry partnerships mentioned in note 49, supra, both focus on developing continuous manufacturing methods.

\footnote{51} Relative to other industries, equipment is underutilized; in a survey of European drug plants, nearly two-thirds of plant equipment were idle at any given time. Friedli et al., Operational Excellence, supra note 29, at 60. See also Herlant, supra note 27, at 67. Overall equipment effectiveness (the percent of scheduled runtime a piece of equipment produces good products) averages 20–30%, compared to 50–90% in the automotive, consumer packaged goods, aerospace, and computer industries. Bowman Cox, Attention Turns to the Business Case for Quality by Design, Gold Sheet, *5 (2009).

\footnote{52} Pharmaceutical stock turns over on average once to twice per year, where consumer goods typically turn over 16–20 times per year and high tech goods can turn over as high as 50 times per year. Friedli et al., Operational Excellence, supra note 29, at 24–25. Slow turnover creates high inventory costs, likely justified by a desire to avoid losing any possible sales. Id. at 63.

\footnote{53} Xiaojun Wang, Inventory Management in a Pharmaceutical Company: Minimizing Discard Practices, 25–28 (2010). Excessive stocks of materials may be overcautiously (by the company’s own standards) maintained to avoid any possibility of production delays, which can result in significantly higher inventory costs and rates of discarding expired materials. See, e.g., Id. at 54–59 (Finding in an API plant case study that ingredient stocks could be reduced by 43% while still meeting the company’s own stringent requirements for backup supplies.).
Pharmaceutical manufacturing ensures quality by discrete testing, typically at the end of production stages, to identify out-of-specification products which must be discarded, instead of continuously monitoring product characteristics to guarantee quality throughout production. As a result, pharmaceutical manufacturing processes have much higher error rates than permitted by regulation in final products. This combination—a lack of ongoing quality management and very strict final product standards—leads to very high levels of unacceptable final product relative to other industries: between 7% and 16% of final products must typically be discarded. In other industries with well-developed manufacturing, even those with less strict final product standards, manufacturing processes typically are significantly more robust throughout, requiring less end testing and fewer product discards. The unpredictability inherent in end-oriented stringent testing have both economic and human costs. A faulty product that makes it to the end of the production line before testing can contribute to either both drug shortages, if the batch is discarded, or product recalls, when testing fails to catch the problem before distribution.

One consequence of guaranteeing product quality by testing is that the testing itself takes a long time and disrupts manufacturing. This has especially large effects because FDA requires that any out-of-specification test result be addressed by a full investigation before either re-testing to validate the result or continuing the manufacturing process. Quality control thus both consumes a large portion of manufacturing time and creates tremendous variability in cycle time, which itself leads to other inefficiencies. In one plant with an average production time of 250 days, a stunning 237 of those days were used for quality assurance and quality control.

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54 Labor value-add time (how much time is spent adding value to the product), is typically around 20% in a pharmaceutical plant; in the automotive industry, value-add time is typically around 60–70% or higher. Cox, Attention Turns to the Business Case for Quality by Design, supra note 51, at *5. The ratio of direct labor (people actually making drugs) to indirect labor (management, quality control, and engineering) is roughly ten times lower than in other industries. Id.; see also FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 57.

55 FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 75. Continuous monitoring is different from continuous manufacturing; the former involves constantly measuring product quality during manufacturing processes, while the latter describes the difference between a constant-in/constant-out assembly-line system and one where large batches of a product go through separate sequential process steps.

56 Id. at 76.

57 Id.;

58 Yu, supra note 35, at 782; see infra Section I.C.2.

59 FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 72.

60 21 C.F.R. § 211.192.
This dire picture is not universal. Some industry leaders have embraced some modern manufacturing techniques, with concomitant gains in efficiency and continuous control over drug quality. But even those leaders face substantial barriers to innovative change. Overall, manufacturing tends to be highly inefficient and non-innovative compared with other industries and with earlier stages in the life of a drug, with major implications for the industry, the healthcare system, and society as a whole.

C. Potential benefits of improvements

Manufacturing innovation can lead to major improvements. The potential efficiency gains have frankly stunning monetary and health implications. Gains to drug quality and reliability have less quantifiable but also important implications for the health.

1. Reduced costs

Tens of billions of dollars are spent annually on manufacturing inefficiencies. Efficiency increases consequently carry large potential benefits. Suresh and Basu found potential yearly savings of $19 million in COGS for a single billion-dollar blockbuster drug, with lifetime revenue increases of $577 million. They also collected estimates of potential savings to the pharmaceutical industry worldwide ranging from $15 to $90 billion yearly.

Vernon and colleagues have analyzed the potential social gains from industry-wide drug manufacturing efficiency improvements. Vernon describes two possible boundary scenarios resulting from various hypothetical increases in manufacturing efficiency, which would decrease the marginal cost of producing drugs. In the first scenario, lower

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61 FRIEDELI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 125–26. See also Wang, supra note 53, at 14 (describing the process for manufacturing the main active ingredient for Schering-Plough/Merck’s cholesterol drug Vitorin as including 21.7 days of manufacturing cycle time and 63 days of time required for testing and quality control/quality assurance).

62 See, e.g., FRIEDELI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 82–130.

63 Basu et al., supra note 22, at 186. Revenue increases include the effect of earlier peak drug availability.

64 Id. One early-moving major drug company, GlaxoSmithKline, has estimated that its own ongoing program of optimizing manufacturing operations will deliver annual pre-tax savings of approximately $4.5 billion by 2014. GlaxoSmithKline 2011 Annual Report 55, supra note 20. The program cost approximately $7.7 billion to implement. Id.

65 Vernon et al., supra note 11.
manufacturing costs result in lower prices to consumers. In fully competitive markets where marginal price equals marginal cost at equilibrium, this should occur. However, even in monopolies or oligopolies when profit-maximizing firms have the ability to price above marginal cost, orthodox economics predicts that lower manufacturing costs will decrease prices, resulting in consumer surplus.\footnote{Vernon’s second boundary case, manufacturers stray from the orthodox market model by holding prices steady.\footnote{Id. at 234–37.} The resulting increased cash flow from sales would tend, both theoretically and empirically, to increase firm R&D expenditures.\footnote{Id. at 234–37.} An industry-wide 20\% decrease in manufacturing costs, if prices hold constant, would lead to a $3.9 billion one-time increase in annual R&D flows; the present value of that increase, taking into account patterns of R&D growth over time, is $110.4 billion.\footnote{Vernon et al., supra note 11, at 236, Table 2.} Increases in pharmaceutical R&D, in turn, have large effects on social welfare, since newly discovered drugs can improve health outcomes and improve life expectancy; Lichtenberg has estimated that each $1,345 invested in pharmaceutical R&D leads to health increases with a value of one U.S. life-year.\footnote{F. R. Lichtenberg, Sources of US Longevity Increase, 1960-1997 (National Bureau of Economic Research, 2002), available at http://www.nber.org/papers/w8755.} Using this estimate, Vernon calculated that the 20\% reduction in manufacturing costs would, through increases in R&D spending, result in an annual gain of 5.7 million life-years.\footnote{Vernon et al., supra note 11, at 236, Table 3.} Using a

\[\text{price} \text{ making} \text{ do} \text{ in} \text{ making} \text{ drugs} \]
benchmark approximate value of $100,000 for a life-year, the annual value of this health increase would be $574 billion.\textsuperscript{74}

Even though Vernon’s two estimates are stylized, the social gains of even moderately increased pharmaceutical manufacturing efficiency are to be measured in the tens or hundreds of billions of dollars, and it seems clear that there is room for significantly more than moderate gains.

2. Improved quality

In addition to lowering costs, manufacturing innovation can improve drug quality. Innovative processes that ensure quality throughout the production process can increase final drug quality more cheaply and effectively than increased end-stage testing, largely because drug production is currently far less developed and exacting than drug testing.\textsuperscript{75} Resulting improvements in drug quality could have a major effect on human health and well-being, especially in reducing two major related concerns: quality failures, such as contamination events, and drug shortages.

Contamination events, or other major quality control failures, cause loss of life and decrease confidence in the industry, which may itself have health ramifications.\textsuperscript{76} Such quality failures include the Chinese heparin crisis of 2008 that killed over 81\textsuperscript{77} and 2012’s meningitis outbreak from contaminated steroids which has so far killed 58 and sickened 745 across 20 states.\textsuperscript{78} The use of outdated and decrepit manufacturing equipment directly contributes to the likelihood of contamination events and quality
problems. The absence of forward-looking innovation also contributes.
Greater process understanding, increased in-line monitoring, and more modern techniques all can create higher-quality and safer drugs. For instance, some modern techniques can monitor the uniformity and concentration of ingredients in drug tablets, rather than merely testing a very few samples at the end of production; however, most companies have yet to embrace this type of innovation, in part for the reasons described below.

Improving manufacturing can also help alleviate drug shortages. Drug shortages are an ongoing and increasing problem estimated to have monetary costs totaling $416 million per year, and unknown human costs in terms of patients dying, suffering adverse reactions, or delaying treatment. In 2011, 73% of shortages were sterile injectable drugs, many of which are important front-line cancer treatments in widespread use, but shortages exist across all dosage forms. The ultimate causes of

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79 See Margaret Hamburg, Speech to the Annual Meeting of the Generic Pharmaceutical Manufacturers Association (2013), available at http://www.fda.gov/NewsEvents/Speeches/ucm340870.htm (last visited July 26, 2013) (stating that “unfortunately, we’ve seen far too many quality lapses throughout the pharmaceutical industry over the past few years,” connecting quality problems to “aging facilities,” and noting that quality concerns are “equally important for . . . future pipeline[s].”).

80 See, e.g., Eunah Lee et al., High-throughput Analysis of Pharmaceutical Tablet Content Uniformity by Near-infrared Chemical Imaging, 21 SPECTROSCOPY 24 (2006).

81 A drug shortage is “a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level.” U.S. FDA, Drug Shortage Manual of Policies and Procedures, 7 (2012). In 2011, there were 267 such drug shortages, up from 211 in 2010, 166 in 2009, and 61 in 2005. K. Bom, Time and Money: An Analysis of the Legislative Efforts to Address the Prescription Drug Shortage Crisis in America, 33 J. LEGAL MED. 235, 237–38 (2012). The trend is expected to continue, with even more shortages expected in the future. Id.


84 Woodcock & Wosinska, supra note 44, at 170.


86 S. L. Kweder & S. Dill, Drug Shortages: The Cycle of Quantity and Quality, 93
drug shortages are debated, but most are closely linked to manufacturing problems. In 2011, 46% of drugs shortages were caused by quality issues, “including bacterial or mold contamination, tablet disintegration, and the presence of foreign particles such as glass or metal in vials,” and 19% were caused by manufacturing delay or capacity issues, “for example, when embedded quality problems with one product forces closure of a production line or facility for repairs, resulting in shortage of other products (even those for which no quality problems had been detected).” Manufacturing innovation and improvement to increase robustness, flexibility, and drug quality can significantly help shortages.

The human costs of manufacturing failures are large and apparently increasing. Improving innovation in manufacturing can help to reduce the incidence of manufacturing quality failures, especially those which result in harmful contamination events and direct human injury. Manufacturing innovation and the increase in quality and flexibility can also reduce the incidence of drug shortages. More speculatively, beyond the avoidance of drug manufacturing failures, more reliable and better controlled manufacturing could increase drug uniformity and quality, potentially improving the predictability of medical treatment. Overall, manufacturing innovation has the potential for major human health benefits as well as the cost benefits available to the industry—which may themselves translate into other health benefits.

II. THE FAILURE OF INNOVATION POLICY IN PHARMACEUTICAL MANUFACTURING

As described above, innovation in drug manufacturing is vital for a well-functioning health system. This innovation landscape is deeply shaped by legal rules and regulatory structures, which are responsible for much of the paucity of innovation. The limited literature which has previously noted innovation problems in pharmaceutical manufacturing has focused largely
on firm culture and executive focus. While there is undoubtedly some truth to these explanations, the role of legal rules and innovation policy in slowing innovation has gone unrecognized in the literature on innovation theory. As a practical consequence of that theoretical lacuna, calibrated policy successfully drives innovation in drug discovery and development, but not in drug manufacturing.

Similar to drug discovery and development, innovations in drug manufacturing are frequently expensive to develop but relatively easy to copy once known, making them appropriate targets for intellectual property incentives. However, the intellectual property exclusivity incentives available for manufacturing innovation are less effective, and have more serious negative effects on innovation, than those available for drug discovery and development.

89 See, e.g., FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 32 (“Manufacturing has not been seen as central in producing competitive advantage.”); Cox, Attention Turns to the Business Case for Quality by Design, supra note 51 (citing Ted Fuhr, pharmaceutical consultant at McKinsey & Co.). Other institutional factors, identified in these sources as well as in conversations and interviews with pharmaceutical industry consultants, executives, and in-house and outside counsel, may involve the typical background of pharmaceutical company executives in R&D or sales rather than in manufacturing, the greater ease of promoting R&D advances to shareholders over manufacturing improvements, and differences in training between manufacturing/operations personnel and R&D personnel.

In addition, given the realities of limited management capital and attention, management may focus exclusively on incentives for drug discovery innovation which tend to exceed those available for manufacturing innovation. See, e.g., FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 154. (“As long as gross margins on drugs are as high as today, questions on intellectual property are overriding the question of manufacturing costs.”) See also Girish Malhotra, Profitability through Simplicity: Financial Justification for QbD and Cost of Regulation Compliance, PROFITABILITY THROUGH SIMPLICITY (2012), http://pharmaceuticalcoatings.blogspot.com/2012/05/financial-justification-for-qbd-and.html (last visited February 6, 2013) (“Strategic manufacturing, technology innovation, higher profits and shortened time to market are the QbD drivers. Industry should have been there fifty plus years ago, but the current blockbuster business model absorbed all of the manufacturing deficiencies, and shareholders got accustomed to the fast paced introduction of new drugs and profits.”). Blockbusters may have both higher potential profits and lower manufacturing costs than other drugs. High volume means fixed costs are lower per unit. Marginal costs may also decrease due to economies of scale, especially for simply formulated small-molecule drugs. Thus, if blockbusters are management-paradigm-defining, effort will tend to be focused away from manufacturing innovation. While these business and organizational factors may play a significant role alongside legal factors, a full accounting of them is far outside the scope of this piece.

90 See infra Sections II.B.1.b and II.B.3. The same may be true for manufacturing in most industries. However, other industries generally do not need as large incentives to overcome the major regulatory hurdles faced by drug manufacturers, as described throughout Section II.B.
Also like drug discovery and development, drug manufacturing is tightly regulated to ensure public safety. However, while regulatory structures create incentives for innovation drug discovery and development, and also interact cooperatively with intellectual property to strengthen those incentives, regulatory oversight actively inhibits innovation in drug manufacturing.

A. Regulatory hurdles to innovation

Innovation in the pharmaceutical industry occurs against a backdrop of pervasive regulation. In the context of drug discovery and development, the regulatory system provides significant incentives for innovation. Most directly, FDA is statutorily authorized to provide market exclusivity as a reward to drug companies for certain behaviors. FDA’s regulatory oversight also provides an indirect incentive to innovation. Firms develop drugs in several stages, typically taking the drug through three Phases of clinical trials as an Investigational New Drug (IND), then filing an extensive and expensive New Drug Application (NDA) to win approval to sell the drug. This costly regulatory gantlet creates a barrier to entry which can keep competitor drugs off the market, effectively extending monopoly pricing for the innovator company and increasing the reward for the initial innovation. This effect operates on both pioneer and generic.

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91 See infra Section II.B.2.
92 For a general overview of the drug development and approval process, see MARK P MATHIEU, NEW DRUG DEVELOPMENT: A REGULATORY OVERVIEW (2008). Biologics require a Biologic License Application (BLA) instead of an NDA.
94 Pioneer companies can compete in the market for a drug class despite patent protection or regulatory exclusivity preventing them from making an identical drug. For example, Lipitor, the all-time top-selling drug, is a statin, a class of drugs used to reduce cholesterol. Four other branded statins with similar methods of action have also been widely marketed: Zocor, Leschol, Baychol, and Pravachol. P. Kanavos et al., Product Differentiation, Competition and Regulation of New Drugs: The Case of Statins in Four European Countries, 28 MANAGERIAL & DECISION ECON. 455, 457 (2007). Each additional new drug faced the same expensive regulatory hurdles to obtain marketing approval but entered a market with entrenched competition. In a study of statin market share in four European countries, the first statin on the market maintained higher market share and higher prices for a period after the entry of branded substitute statins, but all statins gradually converged to similar market shares, with some price differentiation remaining. Id. at 459–61. Thus, later market entrants face lower revenues but the same high regulatory approval costs; this acts to deter the marginal market entrant (a hypothetical sixth branded statin). For very large markets like statins, the hundreds of millions of dollars for regulatory approval may be balanced by potential profits; for smaller markets, the same regulatory costs are correspondingly more important, deter more
Finally, as discussed below, the FDA approval process strengthens the exclusivity effects of drug patents by making them much harder to invent around.\footnote{See infra Section II.B.1.}

In the context of drug manufacturing, on the other hand, FDA not only fails to create incentives for innovation, it imposes significant limits on innovation.\footnote{I do not claim that FDA’s innovation-dampening effect is deliberate. The reasons behind specific manufacturing regulations may be the subject of future work. Notably, regulations which block innovation run contrary to the common story of administrative agency capture by the regulated industry. For a brief description and helpful notes on agency capture theory, see DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 36–43 (2010)}

First, innovation during the NDA process is constrained by institutional resistance to approving novel technologies; as a result, firms avoid innovative technologies in NDAs for fear of delays in receiving marketing approval. Second, some aspects of manufacturing are mandated by current Good Manufacturing Practices (cGMP) regulations, which create \textit{de facto} technological standards that are not subject to firm-level innovation. Third, post-approval changes in manufacturing are hampered by procedural hurdles of regulatory filings, known as supplemental NDAs (sNDAs), and by substantive hurdles of regulatory lock-in of manufacturing methods determined early in development. These regulatory constraints are generally imposed without considering their impact on innovation and efficiency.\footnote{FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 126 (“[I]n life sciences operations[,] . . . the tendency is for compliance requirements to be imposed upon operations without adequate consideration for the effectiveness of the method or the implications on the overall process flow.”)}

1. Pre-approval barriers

The first and perhaps most pervasive barrier to innovation arises before approval and reflects a combination of typical agency practice and market dynamics, which together heavily dissuade firms from including novel technologies in NDAs. An NDA—or an Abbreviated New Drug Application (ANDA) for a generic—must include “a full description of the competition, and thus preserve monopoly or oligopoly pricing power.\footnote{The costs of generic approval are much lower, but so are potential profits, so the regulatory barrier to entry remains significant. Eisenberg, The Shifting Functional Balance Of Patents And Drug Regulation, supra note 94, at 121. The first generic entrant can in some circumstances obtain a 180-day window of exclusivity which tremendously increases generic profits, since the generic company usually sells its drugs at near-monopoly prices within that window. Id. at 122. However, no other generic companies have the benefit of this extra profit.}
methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug” which must be approved by FDA.\textsuperscript{99} The agency has historically been reluctant to accept unfamiliar technologies, especially in NDAs.\textsuperscript{100}

For example, for roughly a decade beginning in the 1960s, several companies filed NDAs including manufacturing controls which used a technique known as high performance liquid chromatography (HPLC).\textsuperscript{101} At the time, HPLC was considered technically superior to the previously dominant technology, thin-layer chromatography.\textsuperscript{102} However, FDA was familiar with the older technology and had approved its use before; in addition, it was used in the United States Pharmacopoeia, a source of drug standards.\textsuperscript{103} FDA reviewers were relatively unfamiliar with HPLC. As a result, getting approval for an NDA which included HPLC was nearly impossible for that decade; firms had to replace HPLC with an alternate technique to receive approval.\textsuperscript{104} Eventually, FDA was persuaded to accept HPLC as a validated technique, and it is now widely used.\textsuperscript{105}

HPLC provides an early example of trying to get new technology approved after FDA’s entry into tight regulation of manufacturing, and stands out for the persistence of firms trying to get the technique approved. Firms have now learned from the HPLC experience and other similar situations: even if a sponsor can eventually get FDA to accept a novel technology, that innovation comes with a built-in risk of major delay in getting approved. This delay has very high costs for sponsor companies, because delay in getting approval cuts into the patent-protected period of market exclusivity during which brand companies make the vast majority of their profits.\textsuperscript{106}

Consequently, companies have very strong incentives to avoid incorporating any new technologies in NDAs. A Pfizer executive testified about this effect to FDA, describing an initial NDA draft which included two parallel ways to measure a drug characteristic: one required shipping a sample 3,500 miles from Ireland to New Jersey and took a week to get

\begin{itemize}
\item \textsuperscript{99} 21 U.S.C. § 355(b)(1)(D), 21 C.F.R § 314.50(d)(1); for ANDAs, see 21 U.S.C. § 355(j)(2)(A)(vi) and 21 C.F.R § 314.94(a)(9)(i).
\item \textsuperscript{100} For a persuasive account of FDA’s risk-aversion as based in concerns of personal and individual reputation, see CARPENTER, supra note 98, at 67–68
\item \textsuperscript{101} Hussain interview, supra note 1.
\item \textsuperscript{102} Id.
\item \textsuperscript{103} Id.
\item \textsuperscript{104} Id.
\item \textsuperscript{105} See, e.g., GEORGE LUNN, HPLC METHODS FOR RECENTLY APPROVED PHARMACEUTICALS (1st ed. 2005) (Detailing HPLC methods for assays of hundreds of recently approved drugs).
\item \textsuperscript{106} CARPENTER, supra note 98, at 637
\end{itemize}
results, and one could be done on-site in the manufacturing plant in a matter of minutes. Due to worries about regulatory delays and associated costs, Pfizer removed the second, innovative method from the NDA, declining to risk delay in trying to get the new technique approved. This practical barrier to pre-approval innovation, even though not based in explicit FDA policy, consistently keeps novel technologies out of NDAs. Since other regulatory barriers to innovation, discussed below, create hurdles to changing manufacturing procedures post-approval, this pre-approval barrier has effects which persist throughout the lifetime of a drug.

2. Current Good Manufacturing Practices

The second type of barrier comes from the requirement that drugs be manufactured in compliance with cGMP regulations. Innovation theory recognizes that innovation can be stifled when regulators require the use of specific technologies. FDA generally avoids technology mandates—although cGMP regulations contain rigorous requirements on all aspects of drug manufacturing, including ventilation of production buildings, equipment maintenance and cleaning, and production and control records for each batch, these requirements are goal-oriented performance standards. However, industry effectively creates de facto technology

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108 Id.
109 21 U.S.C. § 351(a)(2)(B) (“A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform . . . current good manufacturing practice.”)
111 21 C.F.R. §§ 211.46, 211.67, and 211.188, respectively.
112 See, e.g., 21 C.F.R. § 211.63, Equipment design, size, and location (“Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.”). One exception is an organizational mandate that the quality control group must be separate from the manufacturing group. 21 C.F.R. § 211.22. Manufacturing personnel are thus frequently less focused on regulatory quality, and quality control personnel understand manufacturing less well and are less likely to seek regulation-compliant innovative changes. Hedley Rees, Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics 120–22 (2011). Quality control enforces regulatory requirements rather than seeking generally to improve quality. Id.
mandates by adhering tightly to technical examples in guidance documents. This effect is more severe than the common practice of treating guidance as effectively binding, because rather than adhering to the agency’s principles, industry adheres to technical examples which narrow the diversity of acceptable technologies.

The most pervasive example of this dynamic comes from industry reaction to FDA’s 1987 Guideline on General Principles of Process Validation. That guidance, which described the way companies should validate processes including manufacturing methods, stated the principle that “[t]ests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results.” But to illuminate this broader principle, FDA included a single example: “For example, the AAMI Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices approved 2 December 1981, states: ‘The performance qualification should include a minimum of 3 successful, planned qualification runs, in which all of the acceptance criteria are met.” From this example, and just a few others mentioning three validation batches in roughly contemporaneous guidances, industry almost uniformly accepted a procedure by which exactly three batches are used for validation of every process—whether or not three batches is actually “a sufficient number of times to assure reliable and meaningful results,” as the guidance’s principle requires. This three-batch regimen continues today, though FDA has recently sought to roll it back, and in 2011 replaced the 1987 guidance altogether.

Industry thus self-imposes technological standards by adhering to guidance examples over principles. This self-limitation is based in desire to avoid regulatory delay or uncertainty, and in designing for regulatory compliance instead of quality. Like other technological standards, it hinders innovation. FDA has recently sought to deal with this industry-

113 Guidance is explicitly non-binding, and includes disclaimers to that effect. See, e.g., Guidance on Out-of-Specification Results 2, supra note 14.
115 Id. at 16.
116 Id.
117 See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm (noting that industry adopted a 3-batch standard based in part on the 1987 Guidelines, and noting that the 3-batch standard should not be generally applied).
119 See, e.g., JOHN AVELLANET, GET TO MARKET NOW! TURN FDA COMPLIANCE INTO A COMPETITIVE EDGE IN THE ERA OF PERSONALIZED MEDICINE 187 (2010); (“Quality systems do not exist for the sake of quality . . . quality departments exist to implement and maintain the quality system required by regulatory health agencies and regulations.”).
imposed restriction by simply refusing to include examples in guidance documents;\textsuperscript{120} other innovation-increasing changes may shift industry behavior from this pattern as well.


Innovation in manufacturing can also take place once a drug, and its attendant manufacturing method, has already been approved. The process of continual improvement is central to manufacturing efficiency in other industries, and larger, discrete innovations can also be incorporated to improve production. The intuition that manufacturers making a product for years should be better at it—from experience gained and applied through process tweaks and improvements—relies entirely on post-approval manufacturing innovation. In the petroleum processing industry, for instance, continuous improvement of larger discrete processing inventions has been as valuable as the discrete inventions themselves.\textsuperscript{121} However, this process of improvement in drug manufacturing faces substantial hurdles from FDA, both procedural barriers in the form of regulatory filings and substantive barriers in the form of regulatory lock-in based on the empirical basis of persistent drug specifications.

a. Procedural barriers

The regulatory hurdles to manufacturing innovation most readily cited are procedural barriers to manufacturing change which arise from FDA’s requirements that manufacturing changes be registered and approved.\textsuperscript{122} After receiving marketing approval, a sponsor must notify FDA if it makes any changes to an approved application.\textsuperscript{123} Changes are


(“When the SUPAC equipment addenda were published with tables referencing specific equipment, the tables were misinterpreted as equipment required by FDA . . . Therefore, this revised draft SUPAC addendum . . . no longer includes tables referencing specific equipment.”).


\textsuperscript{122} FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 71.

\textsuperscript{123} Major notifications come in the form of a Supplemental New Drug Application (sNDA).
categorized as major, moderate, or minor. Substantial regulatory submissions are required for major and moderate changes, and major changes require agency preapproval before implementation. Any manufacturing change that “may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance” is a major change. Minor changes must be detailed in an annual report. For changes in any category, the drug sponsor must evaluate the change’s effects on product safety and efficacy and show those effects through appropriate studies to determine whether a supplement is needed.

The procedure for getting these changes approved is costly. In addition to the actual costs of preparing and submitting a manufacturing supplement, time is required to prepare the supplement and to receive a decision from FDA. Perhaps more important, a supplement raises risks, both that FDA might not approve the submission—which decreases the expected benefit of a change—and that FDA might reopen previously approved and settled manufacturing issues and find new problems to be solved.

Overall, this system creates a substantial regulatory burden imposed on any type of manufacturing innovation, with correspondingly larger burdens for larger changes. Such procedural costs, when applied to every manufacturing change, place an enormous burden on FDA, which has been “overwhelmed by the number of [manufacturing] supplements filed in recent years.”

124 21 C.F.R. §§ 314.70(b), (c), and (d), respectively.
125 21 C.F.R. § 314.70(c). Moderate changes include changes to the container closure system that do not affect drug quality, 21 C.F.R. § 314.70(c)(2)(i); removing a test or relaxing a requirement to comply with an official drug compendium, 21 C.F.R. § 314.70(c)(2)(iii); and, for biologics, changes in production scale that involve changing equipment or replacement of equipment with differently designed equipment which does not otherwise change the production process, 21 C.F.R. § 314.70(c)(2)(ii)(A)–(B).
126 21 C.F.R. § 314.70(b)(3). In addition to the actual regulatory procedural hurdles, the requirement of regulatory submissions creates intra-firm hurdles, because innovative ideas must be transferred from the manufacturing department to the separate regulatory compliance department.
127 Major changes have “a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.” 21 C.F.R. § 314.70(b). They also include changes to the formulation or specification of the drug, including inactive ingredients, 21 C.F.R. § 314.70(b)(2)(i).
128 21 C.F.R. § 314.70(d).
130 Applications also burden FDA, which has been “overwhelmed by the number of [manufacturing] supplements filed in recent years.” Yu, supra note 35, at 782. In 2005 and 2006, the Office of Generic Drugs alone received over 3,000 such manufacturing change supplements. Id.; over 1,600 supplements were filed for branded pharmaceuticals, and over 800 for biologics. U.S. FDA, “Manufacturing Supplements” in FY 2008 PDUFA Performance Report, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm209404.htm (last visited July 26, 2013). Of the latter two sets,
change, may completely prevent the type of continuous improvement which has been so successful in driving efficiency in other industries.\(^\text{131}\) Finally, in addition to changing the cost-benefit calculus to disfavor small innovations, across-the-board increased change costs likely create a mindset that all changes are to be avoided as not worth the trouble and unprofitable; this may shift effort away even from larger, net-beneficial innovations.\(^\text{132}\) This reality of procedural barriers is also in significant tension with the underlying theoretical goal that Good Manufacturing Processes be “current.”\(^\text{133}\)

Overall, procedural barriers are a major limitation to manufacturing innovation, particularly with respect to implementing new techniques and procedures. Because every manufacturing change involves a significant regulatory cost in terms of money, time, and uncertainty, all innovation becomes less likely.\(^\text{134}\) From a structural perspective, a central pillar of

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\(^\text{131}\) See Yu, supra note 35, at 782 (“[T]he burdensome regulatory requirements of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous ‘real time’ assurance of quality.”).

\(^\text{132}\) See FRIEDLI ET AL., OPERATIONAL EXCELLENCE, supra note 29, at 160 (“[T]he high-level of regulation has hindered pharmaceutical companies to continuously improve their processes. However, we sometimes had the impression that many pharmaceutical production managers use the high level of regulation as an excuse for not having achieved any significant process improvements over the years.”).

\(^\text{133}\) According to FDA,

The flexibility in [cGMP] regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the “c” in cGMP stands for “current,” requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been “top-of-the-line” to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today’s standards.

Center for Drug Evaluation and Research, Manufacturing - Facts About Current Good Manufacturing Practices (cGMPs), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm (last visited March 16, 2013). This theoretical requirement for continuous improvement is heavily contradicted by both agency and industry practice as described throughout this piece.

\(^\text{134}\) Procedural expenses are not unique to the pharmaceutical industry, but are lower even in other closely-regulated industries. In the aeronautics industry, for example,
manufacturing innovation in other industries is continuous improvement through frequent small optimizing changes. Those small changes are the least likely to justify the expense of regulatory approval, which may entirely foreclose that path of innovation. However, FDA regulations do not only impose procedural barriers to manufacturing change; they also create substantive barriers to innovation.

b. Drug-specific substantive barriers via regulatory lock-in.

Substantive barriers to change privilege the status quo. These barriers revolve around a requirement for consistency with previously observed values instead of compliance with knowledge-based goals. Medications are approved principally on the basis of clinical trials. FDA’s empirical approval of a drug for use in treating an indication is based on clinical trials using that drug, as it existed when used in the clinical trials. For most drug characteristics, including those which do not affect treatment outcomes or safety, whatever values may exist at the time of regulatory submission become the benchmark for measuring future drugs. Specifications are set without justifying why they should have those values except that those values worked in the relevant clinical trials. In the absence of sufficient understanding, the positive becomes the normative through regulatory entrenchment.

The main implementation of this process is the batch-based generation of drug quality specifications. For some drug attributes, like moisture content or levels of impurities, the acceptable specification for the drug is determined by testing three batches, as described above, of the drug as used for clinical testing. Specifications for the drug are set based on producers of parts for airplanes must obtain Federal Aviation Administration (FAA) approval prior to manufacturing airplane parts. See 14 C.F.R. § 21. FAA must be notified of, and can review, any change in manufacturing procedure that could affect the airworthiness of a part. See, e.g., 14 C.F.R. §§ 21.93–97 (approval of changes to type certificate); 14 C.F.R. §§ 21.139, 21.150, 21.309, 21.320, 21.609, 21.620 (notification and review of changes in manufacturing facilities or quality systems). However, notification and review do not require preapproval, reducing time and cost barriers.

Too often in the past regulatory submission contained limited information concerning the specific root causes of those conditions. As a result, these conditions became regulatory commitments and plant operators were expected to always reproduce exactly those same sets of conditions. This type of operation can be considered a “static manufacturing operation” because it creates a mind-set that “product is approved and validated – do not change.”

See Friedli et al., Operational Excellence, supra note 29, at 25:

See FDA, Guidance for Industry: Dissolution Testing of Immediate Release Solid
the average values and variability of those initial batches. All future batches of the drug are required to meet those specifications.\textsuperscript{137}

For parameters where the industry and FDA truly do not understand what works and why, this approach may make sense, but even in areas where the relevant science is well understood, empiricism-based consistency still controls.\textsuperscript{138} Dissolution provides one central illustration. A drug’s dissolution profile measures how fast the active ingredient releases from the drug product (e.g., a tablet or capsule), and how fast it becomes soluble once released; these help determine how fast the drug will enter the bloodstream.\textsuperscript{139} Based on the empirical approach, the dissolution profile generated from testing initial drug batches is used to establish batch-to-batch consistency in ongoing manufacturing, as well as to evaluate manufacturing changes in scale, site, component and composition, or equipment and process.\textsuperscript{140} Any change—and every batch—must match the specified dissolution profile to be approved.

This approach fails to incorporate the well-developed understanding of differences in solubility between different types of drugs. For highly soluble drugs, dissolving is easy and therefore wide variation is likely to have no effect on the drug’s effectiveness (i.e., some other step, like crossing the gastrointestinal wall, limits the rate of drug action); for low-solubility drugs, dissolution rate may be crucial to the drug’s performance.\textsuperscript{141} For low-solubility drugs, it may well make sense to have tight manufacturing controls, with their attendant costs, to ensure that

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\textsuperscript{137} See id. at 5 (“Once the specifications are established in an NDA, the dissolution specifications for batch-to-batch quality assurance are published in the United States Pharmacopeia (USP) as compendia standards, which become the official specifications for all subsequent IR products with the same active ingredients.”).

\textsuperscript{138} This system and its accompanying incentives may actively discourage the production of detailed drug knowledge, a question for future research.

\textsuperscript{139} Permeability through the walls of the gastrointestinal tract also significantly influences how quickly an oral dosage form enters the bloodstream. \textit{Id.} at 4.

\textsuperscript{140} \textit{Id.} at 8, 11.

\textsuperscript{141} “[C]urrent dissolution acceptance limits are selected based on data from a small number of batches in the context of their ability to distinguish batches with limited regard to clinical relevance.” Yu, supra note 35, at 783 (emphasis added). In contrast, under a more rational approach, \textit{,} highly soluble drugs could have wide acceptance limits, while low solubility drugs may need closer examination in dissolution testing. \textit{Id.}

\end{footnotesize}
dissolution profile are very similar to those of the clinically tested samples. But for highly soluble drugs, where there is no reasonable expectation that even significant dissolution variability would affect drug efficacy, those same manufacturing controls stand in the way of higher efficiency and other process innovation without any corresponding health or safety benefit.

For this type of observationally determined parameter, FDA regulatory oversight locks in the result of initial manufacturing techniques. However, most firms do not optimize initial manufacturing batches, used for clinical trials, for efficient, high-quality large-scale production. Instead, they rush to produce clinical testing batches as fast as possible to speed drugs to market.\footnote{FRIEDLI ET AL., PATHWAY TO OPERATIONAL EXCELLENCE, supra note 39, at 80.} Manufacturing efficiency and controllability are accordingly given much lower priority, and firms tend to avoid making significant investments in manufacturing process development at the stage when clinical trial supplies are being produced.\footnote{See, e.g., REES, supra note 113, at 405–07 Recently, some companies have experimented with developing manufacturing processes simultaneously with major clinical trials, but this requires significant expertise and resources, generally available only to the largest pharmaceutical companies. Basu, The Current State of Pharmaceutical Manufacturing – In Search of Science, supra note 37, at 80. Process development has been estimated to account for as much as 15-30% of R&D costs. Cox, Attention Turns to the Business Case for Quality by Design, supra note 51, at *4.} Low rates of clinical trial success also lead to decreased investments in developing robust manufacturing understanding,\footnote{Ismail Kola & John Landis, Can the Pharmaceutical Industry Reduce Attrition Rates?, 3 NAT. REV. DRUG DISCOV. 711 (2004).} because it is hard to know early whether a drug is likely to proceed to market. Under the traditional model, manufacturing process development thus happens during later (Phase II or III) clinical trials—after most of the drug’s critical parameters have already been largely determined and locked in by characterization of clinical trial supplies.\footnote{VELLANET, GET TO MARKET NOW! TURN FDA COMPLIANCE INTO A COMPETITIVE EDGE IN THE ERA OF PERSONALIZED MEDICINE, supra note 120, at 60. Under a Quality by Design approach, discussed infra in Section III.A.2, manufacturing methods should ideally be largely in place by Phase II.} Overall, regulation stunts innovation in pharmaceutical manufacturing. The crucial distinction is that, unlike in other industries where regulation is aimed at well-understood quality goals and manufacturers can innovate to reach or surpass those goals efficiently, in pharmaceutical manufacturing the quality goals are defined observationally, on the basis of the early, non-optimized manufacturing process itself. Thus pharmaceutical manufacturing is encouraged by regulation to maintain the status quo and prevent changes. A recently increased focus on quality regulations is likely to exacerbate these problems. The Department of
Justice has stated that it plans to take an increased role in enforcing cGMP regulations. FDA has stated in parallel that it intends to make quality enforcement a major focus in 2013, even as the recent past has seen stepped-up FDA enforcement of cGMP and quality regulations. Increased enforcement is likely to encourage risk-averse adherence to old, approved processes rather than innovative change to newer and more robust methods.

The existence of regulatory hurdles, however, is not in itself sufficient to explain manufacturing stagnation. Tremendous regulatory hurdles exist in the pharmaceutical industry in the context of getting drugs initially approved, but firms overcome the hurdles in that context. The lack of innovation in pharmaceutical manufacturing also results in large part from a lack of sufficient innovation incentives, whether sourced from regulatory exclusivity or from intellectual property-based exclusivity.

B. Intellectual property incentives for innovation

Innovation policy in the pharmaceutical industry, shaped by several Congressional acts including the Hatch-Waxman Act, focuses on market exclusivity incentives for innovation in drug discovery and development. Foremost is the patent system, but the pseudo-patent system of FDA-administered statutory exclusivity is also used to augment and modify drug patents. These innovation incentives operate differently at different stages of drug development. Patents, while available throughout the development process, are particularly prominent in protecting early investment. Patents take another strong role after approval in staving off generic drug entry preventing entry until they expire and then by “evergreening,” a set of tactics to extend effective patent production on a drug. FDA regulatory exclusivity, on the other hand, applies only later in

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146 Frimpong, supra note 77. Frimpong recognized the relevant efficiency constraints: “We know, of course, that there are enormous pressures on all parts of the industry to produce drugs more quickly, cheaply, and efficiently, and our message to you is that you cannot sacrifice drug safety in service of these pressures.” Id.

147 Hamburg, supra note 80


149 I recognize that FDA-administered market- or data-exclusivity are not typically considered intellectual property, and lack some aspects of true intellectual property. I choose to include them in this section nonetheless because they function similarly to create exclusivity incentives for innovation.


151 See, e.g., Eisenberg, The Role of the FDA in Innovation Policy, supra note 12, at
the drug development process, once the drug is already approved and enters the market.\textsuperscript{152}

These innovation incentives are much less effective in the field of pharmaceutical manufacturing. Patents on manufacturing techniques involve an increased cost of disclosure coupled with a decreased exclusion benefit because those patents are harder to enforce. FDA regulatory exclusivity is simply unavailable for manufacturing innovations, and as such plays no real role in incentivizing such innovation; as described below, this represents an opportunity for innovation policy.\textsuperscript{153}

Trade secrecy is significantly more important for manufacturing innovation.\textsuperscript{154} Like patent or regulatory exclusivity, trade secrecy creates incentives for innovation by keeping others from copying the innovation and therefore allowing supracompetitive pricing. Trade secrecy is not usually considered as a target for policy levers, likely because the government has a relatively small role in maintaining trade secrecy. Trade secrecy as the primary means of manufacturing innovation protection brings other problems: the unique aspects of trade secrecy—practical limitations, an unbounded timeframe, process-specificity, and limitations on personnel—make it structurally less capable of incentivizing pharmaceutical innovation. In particular, the type of innovation most needed in drug manufacturing, reflecting greater understanding and process knowledge, are particularly poorly suited to protection as trade secrets.

In sum, this section will show that, of the three main incentives for pharmaceutical innovation—patents, FDA market protection, and trade secrecy—only trade secrecy seems to play a major role in encouraging innovation in pharmaceutical manufacturing. But trade secrecy is flawed as an innovation motivator, at least in this context: it lacks the temporal limitations of either the patent system or FDA market protection, and restricts socially useful disclosure, largely preventing cumulative innovation.

\textsuperscript{152} Eisenberg, \textit{The Role of the FDA in Innovation Policy}, supra note 12, at 366.
\textsuperscript{153} See infra Section III.B.2.
\textsuperscript{154} According to a 1994 survey of industry reported by Cohen et al., pharmaceutical firms reported that 68% of process innovations could be effectively protected by secrecy, but only 36% by patents. \textit{WESLEY M. COHEN ET AL., PROTECTING THEIR INTELLECTUAL ASSETS: APPROPRIABILITY CONDITIONS AND WHY U.S. MANUFACTURING FIRMS PATENT (OR NOT) }34, Table 2 (National Bureau of Economic Research, Working Paper 7552, February 2000), available at http://www.nber.org/papers/w7552. For products, the fractions were much closer at 54% and 50%, respectively; \textit{Id.} at 33, Table 1. This presumably refers to secrecy protection in the earlier stages of drug development, since drug details are public by the time a drug is marketed. See Anthony Arandel, \textit{The Relative Effectiveness of Patents and Secrecy for Appropriation}, 30 RES. POL’Y 611, 613 (2001).
which is central to major advances.\textsuperscript{155} Trade secrecy is also least amenable to policy manipulation, as it has little to no government involvement. In the current system, there is scant intellectual property policy encouraging innovation in pharmaceutical manufacturing.

1. Patents

Patents reward invention by allowing the inventor to recoup high up-front costs through a temporary monopoly and correspondingly high prices. In addition, the patent system requires that the knowledge created by the inventor be disclosed to the public; this disclosure is “the quid pro quo of the right to exclude.”\textsuperscript{156} Disclosure not only allows the eventual use of the innovation by the public, but also permits other innovators to use the disclosed information for their own innovations.\textsuperscript{157} The patent monopoly lasts 20 years from the time of filing;\textsuperscript{158} during that time the patentee has the right to exclude others from making, using, or selling the patented invention.\textsuperscript{159} The pharmaceutical industry is a clear outlier in the extent to which patents help drive and shape R&D investment and innovation in developing new drugs.\textsuperscript{160} Both composition of matter patents on drugs and methods patents covering the treatment uses of the drug are important to drug innovation. Composition patents are more valuable because a patent on the active ingredient itself allows the patentee to exclude others from making, selling, or using the drug for any use, even those not specifically envisioned by the patentee.\textsuperscript{161}


\textsuperscript{157} See, e.g., Scotchmer, \textit{supra} note 156. Trade secret law, to the contrary, neither requires nor allows, disclosure of the innovation to the public. \textit{See infra} Section II.B.3.

\textsuperscript{158} 35 U.S.C. § 154(a)(2).

\textsuperscript{159} 35 U.S.C. § 271(a).


\textsuperscript{161} For example, Minoxidil, sold as Rogaine to treat male pattern baldness, was originally developed and sold by Pharmacia and Upjohn to treat high blood pressure. The initial patent on Minoxidil, U.S. Pat. No. 3,461,461 (Aug. 12, 1969) (the ‘461 patent), covered both the compound itself and a method of using it to treat high blood pressure. A later patent, U.S. Pat. No. 4,139,169 (Feb. 13, 1979), covered the method of using Minoxidil to stimulate hair growth. Until the ‘461 patent on Minoxidil itself expired, Pharmacia could prevent others from making or selling Minoxidil, and FDA would not approve any generic version. Once the ‘461 patent expired, generic companies could apply
In striking contrast, patents do little to stimulate manufacturing innovation. Patents on manufacturing processes, which cover using the processes in the United States or importing products made with the processes, do exist in the pharmaceutical industry, but are less valuable and less common than other forms of pharmaceutical patents. Patents fail to drive manufacturing innovation for two reasons: they have structural cost-benefit problems, and, more recently, they may be unavailable for certain important types of manufacturing innovation.

a. Process patent costs and benefits

Process patents have a cost-benefit problem as a meaningful incentive for manufacturing innovation: their costs are too high, and their benefits too low. The cost side is simple: the disclosure of the patent bargain appears too costly a sacrifice of competitive advantage for manufacturing processes. Because processes are hard to observe and hard to determine from the final product, reverse-engineering manufacturing processes is particularly difficult. Thus, in the absence of disclosure, competitors must independently develop the innovation themselves.

On the benefits side, manufacturing process patents are very hard to enforce. First, process patents are usually easier to invent around than to sell generic versions of Minoxidil to treat high blood pressure—which could then be prescribed for any purpose, including treating baldness.

Manufacturing innovation can be protected by process patents on a novel process or by product patents on, for instance, a new piece of equipment. This paper focuses on process patents because they face unique enforcement problems. Equipment patents may help drive innovation in producing that equipment, but the substantial absence of manufacturing innovation suggests these patents are insufficient to drive manufacturing innovation.


Personal conversations with counsel and executives from both branded and generic pharmaceutical companies; see also Cohen et al., supra note 155, at 33–34, Tables 1& 2 (reporting 1994 survey results that pharmaceutical firms considered secrecy effective 68% of process innovations but only 53% of product innovations), but see Mark E. Wojcik, The Perilous Process of Protecting Process Patents from Infringing Importations, 14 Loy. L.A. Int’l & Comp. L.J. 207, 210 (1992) (“Inventors of new drugs created from chemical processes often seek to patent not only the drugs themselves, but the way in which they are produced, in order to secure ‘double’ patent protection.”).

See also Girish Malhotra, Profitability through Simplicity: Are Patents a Double-edged Sword? Perspective Matters., PROFITABILITY THROUGH SIMPLICITY (2011).

See Jeffrey I. D. Lewis & Art C. Cody, Unscrambling the Egg: Pre-Suit Infringement Investigations of Process and Method Patents, 84 J. PAT. & TRADEMARK OFF.
product patents, because infringing a process patent requires performing every step of the process, creating more opportunities for variation to escape patent coverage.\textsuperscript{167} Determining infringement can be particularly challenging because “no one outside the potential infringer knows how the product was made.”\textsuperscript{168} Identifying the manufacturing process from examination of the final product is likely even more difficult for especially valuable general manufacturing methods patents (e.g., methods for performing real-time analysis of production dynamics) compared to product-specific patents (e.g., a method for producing a water-soluble version of the nutritional supplement creatine\textsuperscript{169}).

Once suit has been brought, proving infringement is facilitated by a statutory rebuttable presumption of infringement upon a showing “(1) that a substantial likelihood exists that the product was made by the patented process, and (2) that the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine.”\textsuperscript{170} However, as with identifying infringement, demonstrating a “substantial likelihood” of infringement is likely harder with general than with specific techniques.

For biological manufacturing processes, patent protection strategies...

\textsuperscript{167} Akamai Technologies, Inc. v. Limelight Networks, 692 F. 3d 1301, 1305–07 (Fed. Cir. 2012). See also id. at 32–37 (discussing various laborious investigative steps to support an infringement lawsuit).

\textsuperscript{168} Lewis & Cody, supra note 167, at 7. Identifying international infringement may be particularly challenging.

\textsuperscript{169} Creative Compounds, LLC v. Starmark Laboratories, 651 F. 3d 1303, 1314–15 (Fed. Cir. 2011).

\textsuperscript{170} 35 U.S.C. § 295. If those conditions are met, the burden shifts to the accused infringer to prove noninfringement; “[b]ecause the accused infringer is in a far better position to determine the actual manufacturing process than the patentee, fairness dictates that the accused, likely the only party able to obtain this information, reveal this process or face the presumption of infringement.” Creative Compounds at 1314–15 (citing Lewis & Cody, supra note 167, at 22–23). Although § 295 applies to both foreign and domestic manufacturing, inability to determine the process used is unlikely for domestic manufacturer. See Senate Judiciary Committee Report on the Process Patents Amendments Act of 1989, S. Rep. 100-83, 45 (“[T]he rebuttable presumption would be inapplicable if the defendant has used the process in the United States . . . . In these circumstances, the discovery provisions of the Federal Rules of Civil Procedure and the equitable powers of Federal courts should be sufficient to allow the plaintiff to ascertain what process was employed.”). “[S]ubstantial likelihood” is described in the Report as “less than that of proving successfully at trial by a fair preponderance of the evidence that a product in question was in fact made by the patented process but . . . more than a slight possibility that the product was so made.” Id. at 45.
may differ because manufacturing methods are unusually central for biologics.\textsuperscript{171} Even more so than for small molecule drugs, the manufacturing complexity and development cost for biologics can serve as a potent barrier to entry, keeping competitors off the market. Thus, the public disclosure required by a patent can lower that entry barrier by providing information about both the biologic-specific manufacturing process and general manufacturing processes for biologics, making disclosure particularly unattractive. On the other hand, other firms demonstrably judge the protection of process patents worth the disclosure.\textsuperscript{172} AbbVie has around 200 manufacturing patents protecting the production of Humira, a biologic with over $10 billion in yearly sales used to treat arthritis, and intends to use them to extend its market exclusivity period past the 2016 expiration of Humira’s primary compound patents.\textsuperscript{173}

Overall, patents on manufacturing innovation fail to reward manufacturing innovation adequately. This inadequacy stems from a combination of enforcement difficulties and the problem of disclosing innovative manufacturing methods to competitors.\textsuperscript{174} Firms apparently value the cost of the disclosure as more significant than the speculative benefits to be gained from enforcing process patents.


Despite the structural problems, at least some manufacturing process patents are worthwhile to pursue. But many of these patents have recently been made less valuable. A likely unintended quirk of in the Hatch-Waxman Act has made essentially unenforceable a class of patents covering techniques central to modernizing manufacturing.


\textsuperscript{172} This may be especially true for previously known biologics which are for patent protection as compositions of matter. Manufacturing process patents provide at least some protection.

\textsuperscript{173} Christopher Weaver et al., \textit{Biotech Drugs Still Won’t Copy}, WALL ST. J., *3 (2013).

\textsuperscript{174} An additional lessening of economic incentives may occur from a timing mismatch. For manufacturing methods developed by an innovator firm later in the course of drug development or after the drug has been approved, the value of the innovation is lessened because innovator’s market share of the drug drops sharply on generic entry after expiration of the principal drug patents. This is especially true in the absence of a well-functioning licensing regime, as the innovator firm will be unable to license the innovation to other manufacturing firms and thus cannot capture that potential value.
In authorizing a generic drug approval pathway, the Act created a safe harbor exemption for drugs: it is not an infringing act to use a patented invention “solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”175 The safe harbor was enacted to allow generic drug companies (and now, biosimilar companies) to develop their products, along with required comparability and safety information, before the expiration of the pioneer company’s patent. This lets the generic firm win approval and be ready to market the drug as soon as the pioneer’s patents (or market exclusivity periods) expire.

The techniques potentially implicated by the safe harbor, covering the generation and analysis of data around drug manufacturing, are central to modern manufacturing. They are especially important for biosimilars because biosimilars require extensive analytical testing to demonstrate biosimilarity.176 To the extent that patent protection for such techniques could provide incentives for their development despite the challenges outlined above, those incentives were recently weakened by the Federal Circuit in *Momenta v. Amphastar*.177

*Momenta* turned on making a generic version of Lovenox (enoxaparin), a hard-to-specify mixture of different length sugar chains made by Aventis and used to treat blood clots.178 FDA established five analytically complex and technically challenging “standards for identity” to establish that “generic enoxaparin has the ‘same’ active ingredient as Lovenox.”179 Momenta180 and Amphastar both filed ANDAs for generic

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175 35 U.S.C. § 271(e)(1) states:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.


178 *Id.* at 1349–50

179 *Id.* at 1350–51.

180 Momenta partnered with Sandoz, Inc., (collectively “Momenta) for this joint venture. *Id.* at 1351.
versions of enoxaparin, and Momenta’s application was approved first—an approval worth over $1 billion annually when Momenta’s was the only approved generic.\(^{181}\)

Two days after Amphastar’s ANDA was approved, Momenta sued Amphastar for infringing its patent claiming “methods for analyzing heterogeneous populations of sulfated polysaccharides, e.g. heparin [and enoxaparin],”\(^{182}\) such methods were largely described in and required by one of FDA’s “standards for identity.”\(^{183}\) Momenta alleged that Amphastar was infringing its patent by using the claimed method to show that each commercial batch of its generic enoxaparin was bioequivalent to Lovenox.\(^{184}\) The district court preliminarily enjoined Amphastar from using the technology.

The Federal Circuit reversed on appeal, holding that the safe harbor covers using patents to generate information for submission pursuant to drug regulating laws, whether that submission is for initial approval or related to ongoing manufacturing.\(^{185}\) In fact, the information need never be submitted to FDA, as long as it is “reasonably related” to such a submission.\(^{186}\) FDA regulations require that records associated with a produced batch of drugs be retained for at least a year after the batch’s expiration date, and be “readily available for authorized inspection” at any time.\(^{187}\) The court held that under these regulations, the batch testing data in this case were “reasonably related” to a submission, and therefore Amphastar’s use of the patented process fell under the safe harbor.\(^{188}\)

Modern manufacturing will require increasing amounts of in-line testing, examination of complex product characteristics, and analytical

\(^{181}\) Id.

\(^{182}\) U.S. Pat. No. 7,575,886 (August 18, 2009), col. 4 II.53-55.


\(^{184}\) Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1352

\(^{185}\) Id.

\(^{186}\) Id. at 1353–54.

\(^{187}\) Id. at 1357.

\(^{188}\) 21 C.F.R. § 211.180(a). (c).

\(^{189}\) Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1358. The court distinguished Classen Immunotherapies, Inc. v. Biogen Idec, 659 F. 3d 1057 (Fed. Cir. 2011), which held that the safe harbor does not extend to “information that may be routinely reported to FDA, long after marketing approval has been obtained,”\(^{189}\) by noting that Amphastar’s test batch data “is necessary both to the continued approval of the ANDA and to the ability to market the generic drug. Momenta, 686 F.3d at 1358. The court also held that FDA requires Amphastar to use the patented method to batch-test its enoxaparin for conformity with the identity standards. Id. at 1361.
“fingerprinting” techniques. These methods are neither simple nor cheap to develop, and are relatively easy to copy once known—and are thus paradigm cases for intellectual property. But the current legal regime removes both major policy sources of innovation incentives for such techniques. First, FDA publishes manufacturing testing details within standards for demonstrating bioequivalence or biosimilarity, eliminating the possibility of keeping the process as a trade secret. Second, the safe harbor—as interpreted in Momenta—essentially eliminates the reward of patent-protected monopoly. A vigorous dissent from Chief Judge Rader recognized this expansion of the safe harbor as innovation stifling, describing the decision as “an undeserved victory for those who decline to invest in the expense and difficulty of discovery and invention.”

Momenta will likely have two effects on patent-based innovation incentives under the current regime: (1) decreased investment in manufacturing-diagnostic innovation; and (2) attempts to disclose the bare minimum of information to FDA necessary for approval, with the goal of making it more difficult to copy the novel techniques. This outcome hurts innovation with two consequences. First, innovation in real-time and complex analytical monitoring of manufacturing is crucial for making modern manufacturing more streamlined and efficient, and for obtaining the twin goals of increasing quality while reducing costs. Second, this type of innovation is likely central for driving forward industry-wide improvements, based both on wider adoption and on incremental improvements from the initial innovation.

Overall, process patents on manufacturing techniques are poorly suited to drive innovation in pharmaceutical manufacturing. In addition to basic structural problems—high disclosure costs and challenging enforcement—the safe harbor further reduces the enforceability of continuous monitoring and other evaluative method process patents.

2. FDA-mediated market protection

The second major locus of innovation policy in the pharmaceutical industry lies with FDA. For drug products, FDA is statutorily authorized to grant periods of market protection—market or data exclusivity—in a parallel to the patent system. This protection can be granted as a reward

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190 Judging Momenta on the merits and prognosticating its effects on biosimilar development are both outside the scope of this piece.
191 This exclusivity can be market exclusivity, in which FDA withholds approval from competitors, or data exclusivity, in which competitors cannot rely on the innovator’s data and must spend large sums to generate their own. Though these two types of exclusivity are legally and conceptually distinct, their basic effect—to provide a large and valuable
for winning approval for a new chemical entity, for a treatment for a rare disease, or a new indication, and for conducting pediatric studies. As of 2010, biologics have similar periods of market protection. Finally, in addition to pioneers, protection is also available some first-approved generics or interchangeable biosimilars. This “pseudo-patent” market protection, when in force, may even be more valuable than a patent. It is government enforced and essentially unchallengeable—unlike patents which require expensive private enforcement and are subject to legal challenge—and has various other benefits for pioneer companies.

FDA’s market protection regime creates incentives not only for the discovery of new drugs, but also for the generation of valuable information about drug efficacy through expensive and risky clinical trials. This information is socially valuable but costly for firms to generate, and firms are unable to capture much of the value of the information. FDA promotes information creation both through its initial market approval

innovation incentive—is the same. Accordingly, I will conflate the two forms under the term “market protection.”

Under the Hatch-Waxman Act, five years of market exclusivity are provided for new chemical entities not previously approved for any indication by FDA. 21 U.S.C. § 355(j)(5)(F)(ii).

Passed prior to the Hatch-Waxman Act, the Orphan Drug Act of 1983 grants seven years of market exclusivity for drugs targeting rare diseases affecting fewer than 200,000 patients in the United States. 21 U.S.C. § 360cc(a).

Three years are granted for product changes requiring new clinical trials, including switching to over-the-counter status or adding a new dosage form. 21 U.S.C. § 355(j)(5)(F)(iii).


Under the Biologics Price Competition and Innovation Act of 2009 (BCPIA), Pub. L. No. 111-148, 124 Stat. 119, §§ 7001-03, which creates an abbreviated approval pathway for biosimilars, the reference product is entitled to four years of market exclusivity and an additional eight years of data exclusivity. 42 U.S.C. § 262(k)(7). The 12-year exclusivity period does not apply to relatively minor changes to an approved biologic. Id. An additional six months may be added based on the performance of pediatric studies. 42 U.S.C. § 262(m).


The BCPIA grants follow-on biologics determined to be interchangeable with the reference product, 42 U.S.C. § 262(k)(4), a period of regulatory exclusivity lasting 12 to 42 months during which no other interchangeable product can enter the market. 42 U.S.C. § 262(k)(6).

Eisenberg, The Role of the FDA in Innovation Policy, supra note 12, at 364–66.

Id. at 362–66

Id. at 370.

Id.
process, where approval is indication specific, and through its prohibition on industry promotion of off-label uses without adequate supporting clinical information.\textsuperscript{203}

However, despite the power of FDA’s innovation incentives, they focus exclusively on the process of bringing individual drugs to market. Even those provisions which take effect after the initial market approval, such as exclusivity for changes requiring clinical trials or for pediatric trials, focus on pre-approval-type information and activities: verifying the safety and efficacy of the drug. No FDA exclusivity incentives exist for manufacturing innovation; instead, the only FDA-mediated manufacturing incentive appears to be the ability to avoid the regulatory costs of quality failures and plant shutdowns due to FDA’s regulatory oversight.

3. Trade secrets

Instead of patents or FDA market protection, trade secret protection, grounded in state law, is likely the most valuable form of intellectual property/exclusivity incentive in pharmaceutical manufacturing.\textsuperscript{204} Trade secret law provides protection from misappropriation for information that is reasonably kept secret and derives value from its secrecy.\textsuperscript{205} Trade secrets play a bigger role in protecting manufacturing processes for at least three reasons. First, enforcing manufacturing process patents is difficult, as described above; as long as trade secrets can be kept secret, they do not require monitoring other firms’ activities.\textsuperscript{206} Second, trade secrets, by definition, do not require disclosure of information to competitors which may be broadly useful. Finally, trade secrets, unlike patents or statutory exclusivity, do not have a pre-determined lifespan, and may continue indefinitely. Trade secrets have long been important, and are increasingly so.\textsuperscript{207} Reported cases are relatively rare but provide illustrative examples of

\textsuperscript{203} Id. FDA’s ability to prohibit off-label marketing has come under serious question. The Supreme Court held in 2010 that pharmaceutical marketing is “a form of expression protected by the Free Speech Clause of the First Amendment.” Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2659 (2011). The Second Circuit subsequently held that FDA’s prohibition on truthful speech by pharmaceutical companies about off-label use of FDA-approved products violates the First Amendment. United States v. Caronia, 703 F.3d 149, 166–69 (2d. Cir. 2012).

\textsuperscript{204} Telephone interview with Geoffrey Levitt, Senior Vice President and Associate General Counsel, Regulatory and Policy at Pfizer (November 29, 2012).

\textsuperscript{205} See Uniform Trade Secrets Act § 1(4).


\textsuperscript{207} Robert Graham Gibbons & Bryan J. Vogel, The Increasing Importance of Trade
the possible roles of trade secrets.\footnote{208}

Trade secrets can protect innovation—and consequently provide an incentive to innovate—in multiple ways. At one extreme, a well-protected trade secret on an essential manufacturing technique can completely prevent market entry by competitors and thereby allow monopoly pricing with no predetermined time limit. Trade secrets on manufacturing improvements can also allow competitive cost advantages which change market contours. However, trade secrets can be differently hard to enforce than manufacturing patents; the same secrecy that keeps the innovator company’s intellectual property secret can render the misappropriator’s use of the secret difficult to detect, and can make it hard to determine whether the second firm in fact misappropriated the trade secret or just discovered it independently. And even if trade secrets provide some functional incentive to innovate, they create other difficulties both for the innovation process within a firm and for the spread of social benefits from innovation.

a. Monopoly maintenance by excluding competitors

One example illuminates both the indefinite duration of trade secrets and the difficulty of replicating essential manufacturing techniques. Wyeth manufactures Premarin for the treatment of symptoms associated with menopause, and sells over $1 billion in Premarin yearly.\footnote{209} Premarin is a product of natural conjugated estrogens made from the urine of pregnant mares (“PMU”), and has been marketed without any natural generic substitute since 1942.\footnote{210} Synthetic estrogens exist, but are not FDA-approved as generic substitutes for naturally derived Premarin.\footnote{211} However,
no competitor entered the market, primarily because of the difficulty in extracting the estrogens.

Wyeth extracts and purifies the estrogens from PMU at a plant in Brandon, Manitoba, using a process ("the Brandon Process") it claims as a trade secret. Wyeth obtained several early patents on methods connected with estrogen extraction research; however, these patents provided insufficient information to recreate the Brandon Process, which is itself unpatented. Wyeth took several measures to ensure the secrecy of its process. In fact, the Brandon Process was not written down from 1966, when the plant opened, until 1979, when regulations required the drafting of formal operating procedures.

Several major companies attempted to duplicate Wyeth’s success by extracting estrogens from PMU. All failed. The only other company to successfully extract estrogens, Natural Biologics, did so by acquiring the details of the Brandon Process from a research chemist who had consulted for Wyeth. Natural Biologics had previously failed in its attempts to recreate the Brandon Process by using information from the expired patents as well as manifests of Brandon plant waste chemicals. On learning of Natural Biologics’ plans to extract estrogens using Wyeth’s Brandon Process, Wyeth sued for misappropriation of trade secrets. The district court found misappropriation of trade secrets and a resulting likelihood of hundreds of millions of dollars in decreased revenues and R&D investments for Wyeth if Natural Biologics were to bring generic Premarin onto the market. The court permanently enjoined Natural Biologics from researching or developing any methods for extracting estrogens from urine, or manufacturing any such estrogens.

Wyeth’s trade secret of the precise manufacturing technique for Premarin shows how trade secrets can thwart the intentions of patent law, create deadweight social loss, and hold back manufacturing innovation. The patent bargain is the disclosure of useful information to the public in exchange for a limited period of monopoly pricing to recoup the costs of developing the information. But here, though Wyeth was granted several

213 Id. Wyeth’s estrogen extraction patents included, among others, U.S. Pat. Nos. 2,429,398 (October 21, 1947); 2,551,205 (May 1, 1951); 2,696,265 (Dec. 7, 1954); and 2,834,712 (May 13, 1958). The last patent, the ’712 patent, expired in May 1975. Id.
215 Id. at *3.
216 Id. at *9.
217 Id. at *6–10.
218 Id. at *5–6.
219 Id. at *18, *21.
220 Id. at *25–28.
patents on Premarin, including patents specifically on techniques on extracting estrogens from urine, those patents did not disclose enough information for other firms to recreate Premarin once the patents had expired. Accordingly, Wyeth was able to maintain its monopoly pricing for far longer than the term envisioned by the patent bargain, now for over 70 years, representing an undoubted deadweight loss to society well past the time needed to recoup development costs. Finally, whatever the secret manufacturing method is for making Premarin, that method lacks innovation; FDA defines Premarin by its process, and that definition has not changed—and, in fact, cannot change. In addition, no other firms have been able to innovate cumulatively based on the Brandon Process. No other firms can improve the process of extracting estrogens from PMU, which could potentially lead to better drugs, and no firm can apply the knowledge embodied in that process to developing other processes, whether related to hormones, other drugs, or other fields entirely. Thus, while a monopoly protected by trade is certainly a potent incentive for some manufacturing innovation, it also impedes other innovation in multiple important ways.

b. Non-monopoly incentives and enforcement challenges

Not all trade secrets so completely enforce a monopoly. *Norbrook Laboratories Limited v. H.C. Hanford Manufacturing Company* demonstrates the competitive cost advantage incentives of an innovative manufacturing technique, but also illustrates the challenges of enforcing trade secrets which limit their use as innovation drivers.

Norbrook developed a method of manufacturing veterinary penicillin by conducting the final manufacturing reaction in situ without having to dry the intermediate product. The method was technically challenging, but resulted in tremendous cost savings; the raw materials for the conventional method (which required drying) cost about $56 per kilogram, while the raw materials for the novel method cost only $9 per

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221 See supra note 213 and accompanying text.
223 *Id.* at 469–71. Because the final product is a suspension, the penicillin particles suspended in the injection volume must be small enough to avoid clumping and causing pain when injected but large enough to stay suspended. In the conventional method, two early reagents are mixed, sterilized, filtered, dried, and milled to small particles by a third party; the powder is then sold to the primary manufacturer for assembly into a final dosage form. In the in situ method, the primary manufacturer mixes the early reagents itself and “wet”-mills the product, without filtering or drying, into the final dosage form. Cost savings come from avoiding drying time and avoiding the need for a third-party supplier of the intermediate product. *Id.* at 468–69.
kilogram. The new method was sufficiently different that FDA deemed it a radical shift from the normal method recognized by the United States Pharmacopoeia which required separate approval. Eventually, Norbrook persuaded both the Pharmacopoeia and FDA to approve its in situ method. After approval, the “significant cost advantages” from the new process allowed Norbrook to acquire most of the customers of its competitor Hanford and make significant inroads into the U.S. market for veterinary penicillin.

The process was sufficiently market-changing that Hanford hired Dr. Quinn, the scientist who had invented Norbrook’s procedure (who had subsequently left Norbrook and signed a confidentiality agreement), and induced him to share Norbrook’s trade-secret manufacturing innovation. Once Hanford had acquired the details of Norbrook’s in situ manufacturing process, it was able to implement the process rapidly, without any major changes, and received FDA approval almost immediately.

The details of Norbrook’s discovery of Hanford’s misappropriation illuminate how trade secrecy functions, and fails, in pharmaceutical manufacturing. Norbrook discovered Hanford’s misappropriation essentially by happenstance, not by any monitoring program or FDA notification. After Dr. Quinn left Norbrook, Norbrook sued him in Northern Ireland for unrelated defamation. During discovery, Norbrook uncovered the contacts between Hanford and Dr. Quinn during a deposition of Hanford’s CEO. Norbrook made a Freedom of Information Act request to FDA asking whether Hanford had sought approval to modify its penicillin manufacturing process since Hanford had hired Dr. Quinn. FDA provided a heavily redacted document, and Norbrook investigated further, eventually concluding that Hanford had applied for approval to change from conventional to in situ manufacturing. Norbrook sent a cease-and-desist letter to Hanford and then initiated its suit for

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224 Id. at 469.
225 Id. at 471.
226 Id.
227 Id. at 473.
228 Id. at 474–79.
229 Id.
230 Dr. Quinn had republished a press release by Senator Chuck Schumer, which referenced an FDA investigation into alleged impurities in Norbrook’s veterinary penicillin. Id. at 472. Norbrook had also separately sued Dr. Quinn twice for other breaches of his contractual confidentiality obligations; neither breach related to the in situ technology.
231 Id. at 469, 472.
232 Id. at 469.
233 Id.
misappropriation of trade secrets.\textsuperscript{234} The district court found misappropriation of trade secrets and preliminarily enjoined Hanford from using or publishing Norbrook’s \textit{in situ} process.\textsuperscript{235}

Norbrook’s trade secret thus allows it a significant and continuing market advantage, acting as an incentive for the earlier innovation. However, this case also exemplifies the difficulties of protecting manufacturing processes. Both Norbrook’s discovery that Hanford was using its protected process and its correct inference of trade-secret misappropriation were fortuitous. In many cases, such facts remain undiscovered, rendering trade secrecy’s incentive less certain.

c. Structural problems with trade secrets as innovation incentives

As described above, trade secrets have some advantages for firms over patents; assuming they can be protected, they are indefinite and do not demand disclosure to the public and competitors. However, even well-functioning trade secrets have serious problems when viewed from the standpoint of innovation policy.\textsuperscript{236} First, as long as secrecy is maintained—which can be indefinitely—no other firms, competitors or not, can benefit from the innovation, and society cannot benefit from any cumulative innovation based on it.\textsuperscript{237} A tremendous amount of innovation is cumulative, and a large portion of cumulative innovation is made by firms other than the first innovator.\textsuperscript{238}

Second, the secrecy measures necessary to protect trade secrets may hinder initial innovation even within a firm. To increase secrecy, the trade secret will almost certainly be kept from many individuals at the firm, including other innovators. Even for those who have some access to the information, protection of trade secrets demands compartmentalization and separation of information so that the information needed for an entire protected process can be less easily misappropriated.\textsuperscript{239} Thus, very few

\textsuperscript{234} Id.
\textsuperscript{235} Id. at 489–94.
\textsuperscript{238} See, e.g., Scotchmer, \textit{supra} note 156, at 29–32.
\textsuperscript{239} See, e.g., AVELLANET, \textIT{GET TO MARKET NOW! TURN FDA COMPLIANCE INTO A COMPETITIVE EDGE IN THE ERA OF PERSONALIZED MEDICINE}, \textit{supra} note 120, at 149, describing best practices for trade-secret-related standard operating procedures (SOPs):

Eliminate any intellectual property-revealing step-by-step details. For a
people even within the firm can build on the innovation.

Third, trade secrecy’s limits may restrict its incentives to only some types of innovation. Concerns about departing employees taking trade secrets may disfavor broadly applicable innovations in favor of very product-specific innovations, because fewer competitors could use the specific information and it would be worth less to them. Some innovations are inherently hard to reward through trade secrecy; for instance, since trade secrets are harder to license, a trade secret regime provides lower incentives for innovations which require widespread use by multiple actors (e.g., network effects) to create value for the innovator. These types of broad innovation—topics like sampling techniques, quality analysis, or process workflow—are key to broad improvements in pharmaceutical manufacturing, and unfortunately fit poorly with an intellectual property regime dominated by trade secrets.

Trade secrets are undoubtedly a key tool in protecting pharmaceutical manufacturing techniques. They can completely bar a competitor from the market, or give a market participant a significant cost advantage. However, trade secrets are difficult and uncertain to enforce, and carry significant costs for their possessor in terms of maintaining secrecy and preventing disclosure of the secret. More significantly from a social perspective, trade secrecy prevents the information flow essential for cumulative innovation, and may function poorly for particular types of broad innovation.

Overall, trade secrecy has problems as a primary innovation incentive, and patents and regulatory market protection are either ineffective or unavailable. This absence of incentives is exacerbated by regulatory hurdles to innovation. The innovation deficiency of pharmaceutical manufacturing, with its major attendant problems, is the unfortunate result.

III. NEW DIRECTIONS FOR MANUFACTURING INNOVATION POLICY

As described above, the lack of innovation in pharmaceutical manufacturing is a complex and multifaceted problem. Higher levels of innovation, both within individual firms and across firms through the mechanism of cumulative innovation, would have major benefits for the
industry and the health care system as a whole. The drug industry innovates in drug discovery and development, and other industries innovate in manufacturing; these comparators suggest that drug manufacturing can be a successful target of innovation policy.\textsuperscript{240}

The complexity of the problem, arising from interacting intellectual property and regulatory structures, forestalls a single simple solution. However, the unique role that regulatory oversight plays in creating hurdles to manufacturing innovation—and the contrary role it plays in facilitating innovation in the context of drug discovery and development—suggests that regulatory changes may provide the best policy levers to improve a moribund manufacturing innovation policy.\textsuperscript{241} Some potential changes focus solely on regulatory hurdles, one side of the policy mismatch. Others, however, suggest how regulation can mediate and change innovation incentives, shaping them to drive manufacturing innovation more effectively by encouraging firms to surmount what regulatory hurdles are necessary.\textsuperscript{242} This type of cooperative approach works well in drug discovery and development, and also offers possibilities for innovative manufacturing. One final possibility considers using market quality signals to create incentives for firms. This article does not evaluate other monetary innovation incentives, such as taxes, prizes, and grants.\textsuperscript{243}

\textsuperscript{240} These proposed policy changes address only domestic changes, but have international implications. Drug manufacturing takes place in a global marketplace, though an exhaustive comparative account of global pharmaceutical manufacturing oversight is far beyond the scope of this paper. However, the United States comprised 41.8\% of the global pharmaceutical market in 2011, http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA\%20Figures\%202012\%20Final.pdf (4), and FDA regulates drug manufacturers in 190 countries producing drugs for the U.S. market. Furthermore, other regulatory regimes are broadly similar and similarly inhibit manufacturing innovation. Conversations with Prabir Basu and Hedley Rees. Domestic solutions have the potential for international implications if innovation is developed here and then spreads; that innovation can be regulatory (\textit{i.e.}, the new structures being proposed here), or manufacturing (\textit{i.e.}, the intended results of those new structures). This is particularly true since many markets outside the EU and Japan accept approval of manufacturing changes by FDA without the need for independent review.

\textsuperscript{241} In addition, regulatory changes provide better opportunities for carefully targeting innovation policy, rather than broad shifts in intellectual property which are likely to have cross-industry implications.

\textsuperscript{242} The distinction between these types of changes is not perfectly clear-cut. For instance, proposals to shift procedural hurdles earlier to force earlier manufacturing understanding may push the development of patentable ideas earlier, which would help fix the timing mismatch between drug substance patents and related manufacturing patents, where the latter may be developed too late to capture their full value.

\textsuperscript{243} A rich literature describes these other innovation incentives. For an excellent overview of the literature and a taxonomy of innovation incentives, see DANIEL JACOB HEMEL & LISA LARRIMORE OUELLETTE, BEYOND THE PATENTS-PRIZES DEBATE (Social Science Research Network, SSRN Scholarly Paper ID 2245691, April 1, 2013), available
A. Changes to regulatory structures

Since regulatory oversight imposes both procedural and substantive hurdles to manufacturing innovation, reforming the oversight structure is one clear mechanism to improving innovation. Five different types of regulatory reform could help. First, federal regulatory oversight could be removed entirely, letting states or market and tort systems regulate pharmaceutical manufacturing. Second, FDA could improve innovation by reducing its substantive barriers; one such slowly progressing effort is FDA’s Quality by Design (QbD) initiative. Third, FDA could provide increased regulatory flexibility, loosening procedural barriers to innovative change. Fourth, FDA could change industry development incentives by requiring deeper manufacturing understanding earlier in the development process. Fifth and finally, FDA could provide an independent validation pathway for new technologies, separate from the NDA process.

1. Removing or privatizing oversight

The most radical proposal for addressing regulatory limitations on innovation—but one always available in theory—is to remove regulation entirely. Proponents of such an approach have suggested that FDA be removed from the role of regulating drug development, manufacturing, and marketing.244 This could result in the absence of any oversight at all; however, such an approach—as, for example, before FDA existed—has previously led to enormous quality problems and would likely be unacceptable.245 Instead, oversight would fall to the states or to the market and tort systems.246

Removing FDA’s regulatory power and federal preemption of drug regulation would allow states to regulate drug manufacturing.247 However,
this outcome would likely face fierce opposition from drug manufacturers, who already must navigate the challenge of complying with multiple different national drug regulation regimes.\textsuperscript{248} If such a replacement were to occur, the problem of complying with dozens of additional regulatory regimes would weigh heavily against any possible benefit to innovation.

Alternately, regulation of manufacturing safety could be left to the market. Private certification bodies, instead of FDA, could certify that marketed drugs are safe and effective, as is done today for certain consumer goods. Compliance with private certification could either be left entirely to market mechanisms to establish or could be federally mandated.\textsuperscript{249} Drug manufacturers would submit to an inspection regime run by private certification bodies, which would accordingly certify that products were manufactured according to that body’s standards.\textsuperscript{250}

Several concerns arise from such an approach. First, the protection of consumers from dangerous drugs might be considered too important to entrust to private enforcement. The existence of multiple certification bodies could lead to consumer confusion and the potential for a race to the bottom, where different bodies competed in the market to have essentially laxer standards. Because indicators of drug quality are hard for consumers and doctors to evaluate,\textsuperscript{251} determining which certification body actually rigorously enforced manufacturing standards and which provided only the patina of respectability might be particularly difficult.\textsuperscript{252} In addition, certification bodies themselves might steer clear of the market based on

\footnotesize{\textsuperscript{248} Telephone interview with Geoffrey Levitt, Senior Vice President and Associate General Counsel, Regulatory and Policy at Pfizer (December 20, 2012).
\textsuperscript{249} Campbell, supra note 245, at 9–14.
\textsuperscript{250} This type of mixed private-public regime is employed in other spheres in health care including in hospital certification and Institutional Review Boards. See, e.g., Timothy Jost, Health Law and Administrative Law: A Marriage Most Convenient, 49 ST. LOUIS U. L.J. 1, 9–11 (2004).
\textsuperscript{251} See infra Section III.C.
\textsuperscript{252} Institutional Review Boards (IRBs) provide a useful comparison. These federally-mandated ethics bodies pre-approve research projects with the goal of protecting research subjects. Academic journal editors could potentially evaluate research on ethical compliance, measured by approval by a well-reputed IRB; this would create incentives for strong IRBs. But IRB approval is instead treated as binary—IRB approved or not—and consequently IRBs have proliferated, with a resulting rise in for-profit IRBs, ethical problems, and concerns of IRB-shopping. A similar dynamic could easily arise for drug manufacturing quality indicators. For one critique among many of IRBs in the drug research context, see Carl Elliott, Useless Pharmaceutical Studies, Real Harm, N.Y. TIMES (2011).}
liability concerns. Manufacturing products for sale abroad could encounter major hurdles if manufacturers were certified only by private bodies.

More fundamentally, shifting to private certification bodies might not actually improve innovation in manufacturing very much. Key potential reasons for FDA barriers to innovation would apply similarly to private certification bodies. Private certification bodies would likely have equal or less expertise than FDA, and could easily be equally or more risk averse than FDA. Reliance on drug characteristics as established in clinical trials, as opposed to fundamental science-based specifications, would therefore be just as likely, leading to the same type of substantive barriers to manufacturing innovation.

Practically speaking, removing FDA’s regulatory authority to oversee manufacturing is unlikely. From an industry point of view, any benefit to market forces potentially promoting more efficient oversight might be outweighed by the problem of competing standards. Private bodies could easily face familiar incentives for excessive caution. In addition, given diminished consumer perceptions of the pharmaceutical industry, both consumers and industry may prefer quality oversight by a relatively respected government regulator.

2. Mandated innovation

A second approach involves fixing substantive regulatory hurdles to innovation. FDA has already taken steps toward this goal in its Quality by Design initiative. QbD is a combination of mandated innovation, via FDA requirements of greater understanding and control, and a consequent reduction of substantive barriers arising from the current lack of such understanding.

QbD springs from the concept that “quality cannot be tested into

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253 Campbell, supra note 245, at 15–16.
255 Risky actions by FDA generate backlash, but front-line agents are relatively politically insulated. In a private certification body, the firm and its agents could be subject to private tort liability, leading to increased risk aversion. FDA and its agents are shielded from liability for discretionary decisions by the discretionary function exception to the Federal Tort Claims Act. 28 U.S.C. § 2680(a); see generally Donald N. Zillman, Protecting Discretion: Judicial Interpretation of the Discretionary Function Exception to the Federal Tort Claims Act, 47 ME. L. REV. 365 (1995).
256 Although QbD-like initiatives exist in other jurisdictions, this section focuses on the regulations and guidance issued by FDA and the domestic implementation of QbD.
products; it should be built-in or should be by design.\textsuperscript{257} More pragmatically: drugs are typically manufactured accordingly to a stable, monitored process with efforts to keep parameters highly consistent over time; quality control happens through end-stage testing to identify out-of-specification products. In QbD, production is designed based on scientific understanding and drugs are made in a closely monitored dynamic process, where each stage of the process can be adjusted based on real-time measurements and analyses such that the end result already has a predefined quality level. The aim of QbD is that by the time the drugs roll off the production line, the manufacturer already knows the exact quality of the final product. End-stage testing is used only to verify quality, not to ensure that the products are high-quality in the first place.\textsuperscript{258}

QbD helps ameliorate the substantive obstacles to innovation described above.\textsuperscript{259} If manufacturers have significant knowledge early in the development process, as QbD effectively requires, those drug characteristics which do become regulatorily calcified have a much better chance of being already optimized for long-term manufacturing. More fundamentally, to the extent that deep knowledge of drug products is developed and shared with FDA, that substantive calcification may become less necessary. QbD also has potentially major business benefits even without improvements in regulatory oversight; it is itself a significant source of manufacturing innovation.\textsuperscript{260}

The industry is slowly adopting at least parts of QbD, though with major variation across sectors.\textsuperscript{261} Assessments of QbD adoption differ even within FDA.\textsuperscript{262} FDA has not promulgated regulations enforcing or

\textsuperscript{257} Anurag S. Rathore & Helen Winkle, \textit{Quality by Design for Biopharmaceuticals}, 27 NAT BIOTECH 26, 27 (2009)

\textsuperscript{258} Yu, supra note 35, at 784.

\textsuperscript{259} See supra Section II.A.3.b.

\textsuperscript{260} QbD can potentially increase time and efficiency. In one case study time from dispensing ingredients to market availability decreased from 12 to 4 days, and quality control time was reduced from 8 days to 8 hours, leading to “a major cost-saving and . . . additional assurance that product will pass specification, giving a more predictable supply chain.” Chris Potter, \textit{PQII Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products, 4 J. PHARM. INNOV.} 4, 21 (2009). Potential cost savings between $20 and $30 billion have been estimated. Troubles With Manufacturing: Prabir Basu Explains // Pharmalot, http://www.pharmalot.com/2008/11/the-trouble-with-manufacturing-prabir-basu-explains/ (last visited October 10, 2012). Roger Nosal at Pfizer has estimated that QBD saved Pfizer over $800 million over six or seven years, and suggested that similar amounts could apply to other similar companies. Bowman Cox, \textit{Slogging Toward Quality by Design}, GOLD SHEET, *5 (2012). See also Cox, Attention Turns to the Business Case for Quality by Design, supra note 51.

\textsuperscript{261} See Joanne Eglovitch, \textit{Generic Industry Has Made Progress Implementing QbD, GOLD SHEET} (2013).

\textsuperscript{262} On December 4, 2012, Janet Woodcock, Director of CDER, stated, “I don’t know
requiring QbD, but has stated informally that full QbD implementation is expected in the near future. After this informal statement, the fraction of ANDAs including multiple QbD elements increased from 24.6% in June 2012 to 82.9% in the first half of January 2013. However, these ANDA submissions appear to prioritize QbD form over substance: submissions commonly included a massive amount of information without justification or conclusions, improperly used QbD terminology, or presented prior knowledge without necessary context or justification. Industry still has far to go in actually incorporating QbD methodologies to increase manufacturing efficiency and regulatory efficacy.

QbD techniques are subject to the same forms of market protection as other manufacturing techniques. Firms have shown interest in patenting QbD techniques, though the safe harbor of § 271(e)(1) raises enforceability questions for those patents. Like other manufacturing techniques, though, QbD techniques are largely protected as trade secrets rather than patented and thereby publicized.

how widely QbD will be adopted, because there is a significant upfront investment . . . I think it’s fair to say, we’re not there yet.” Cox, Slogging Toward Quality by Design, supra note 261, at *2. Just three weeks before, Christine Moore, Acting Director of the Office of New Drug Quality Assessment in CDER’s Office of Pharmaceutical Science, stated that “quality by design has really caught on in industry . . . . [T]he science and risk-based approaches in QbD being embraced by pretty much all of the innovator pharmaceutical companies . . . . [W]e’re likely past the tipping point in QbD.” Id. at *3.


265 Id.


267 See supra Section II.B.1.b.

268 See Cox, Slogging Toward Quality by Design, supra note 261. Roger Nosal of Pfizer stated, “One of the things that quality by design has not yielded for most of us is quantifiable value that companies have been willing to share, although we’ve seen bits and pieces from time to time. [Q]uite frankly, . . . people are a little reluctant to say how much they’re saving by doing a quality-by-design approach.” Id. Similarly, Emil Ciurczak, the
In sum, while QbD involves a regulatory mandate to address at least some of the innovation concerns raised above, it is far from a complete solution. Its adoption by industry has been slow and highly heterogeneous, and there is evidence that many companies are adopting QbD in name far more than in practice. To the extent that QbD relies on regulatory compliance rather than innovation incentives, innovation will likely be limited to that specifically demanded by FDA. The one incentive associated with QbD by FDA, and that most relevant to the procedural innovation barriers described above, is the possibility of regulatory flexibility. Unfortunately, that promise has so far proven illusory, as described below.

3. Regulatory flexibility

Allowing greater regulatory flexibility to reduce procedural barriers is a major possibility for improving innovation. This approach has been linked to QbD, but with little effect to date. However, regulatory flexibility is an important potential solution on its own merits.

a. Flexibility and QbD

FDA touted greater flexibility within predefined and well-characterized limits as an advantage of QbD. Rather than a process being defined as a set of rigid steps and measurements with minimum allowable deviation, QbD establishes a process “design space”—a set of parameters within which the firm knows the product being produced is high quality.269 Process changes within an FDA-approved design space should not require regulatory approval.270 This should allow innovation within a defined set of parameters without regulatory hurdles, and would consequently enable more incremental innovation.

However, despite at least moderate progress adopting QbD, regulatory flexibility has failed to materialize. FDA reviewers have

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269 Yu, supra note 35, at 788–89. The design space is the multidimensional space which includes all combinations of parameters resulting in the desired final product. The acceptable range of parameters varies based on the sensitivity of the process outcome to variation in that parameter. Design space is more complex than a set of parameter ranges because different parameters can interact; for instance, a process could be very sensitive to temperature in acidic environments but not in non-acidic ones. Id.

270 Id. at 789.
challenged the type of risk-based regulatory filings expected by QbD, which emphasize tighter controls on risk-linked processes but deemphasize non-risky processes, as insufficiently detailed.\textsuperscript{271} Even though top-level FDA policy may include regulatory flexibility in response to greater knowledge-based QbD filings, it appears that FDA actors on the ground—both approving filings and inspecting plants—have tended to follow the traditional patterns of review rather than adopt the intended additional flexibility.\textsuperscript{272} Given the significant discretion accorded to such front-line regulators and industry reluctance to challenge exercises of that discretion,\textsuperscript{273} implementing flexibility at the ground level may be particularly challenging.

Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at FDA, recently recognized this failure to achieve regulatory flexibility:

\begin{quote}
A quid pro quo people said would really sweeten the deal [was that] if in fact you did QbD, made that investment, then you would have a lot of freedom to operate afterward. I don’t think we have robustly achieved that goal. . . . [O]ver the past decade, the regulations and the regulators have not really adapted that much.\textsuperscript{274}
\end{quote}

FDA Commissioner Margaret Hamburg reiterated this view in February 2013, stating that “in a world where quality risk management is fully embraced, we could foresee a time when enhanced regulatory flexibility might be possible.”\textsuperscript{275} Meaningfully implementing the regulatory flexibility associated with QbD would likely require greater adoption of QbD flexibility principles on the front line and renewed support for that flexibility from FDA policymakers, who now seem to describe it as a foregone possibility.

\textbf{b. Flexibility by certification}

As an alternative to QbD, regulatory flexibility could come from a

\textsuperscript{271} Eglovitch, Regulatory Relief Explored for QbD Use in Post-approval Changes, \textit{supra} note 19, at *6.
\textsuperscript{272} Telephone interview with Hedley Rees, Managing Director, Biotech PharmaFlow Ltd. (March 8, 2013).
\textsuperscript{273} For a detailed description of the dynamics between drug manufacturers and FDA, see CARPENTER, \textit{supra} note 98, at 635–85
\textsuperscript{274} Speech by Janet Woodcock to the IQ Symposium on December 4, 2012, \textit{quoted in} Eglovitch, Regulatory Relief Explored for QbD Use in Post-approval Changes, \textit{supra} note 19, at *2. \textit{See also id.} at *6.
\textsuperscript{275} Hamburg, \textit{supra} note 80 (emphasis added).
new program of voluntary FDA certification of certain manufacturing sites. For sites which consistently demonstrate quality performance above that required by regulation, FDA could approve increased regulatory flexibility. For example, major changes could be implemented with only notice, rather than preapproval. Such a program would allow manufacturers with a record of excellence and high quality production the regulatory flexibility to innovate and continuously improve; it would also provide an incentive to other manufacturers to innovate to achieve that level of excellence and receive the reward of flexibility.

This type of certified regulatory flexibility would not be entirely novel, though it would be new to drug manufacturing. The Occupational Safety and Health Agency (OSHA) runs a similar program, wherein worksites which demonstrate safety excellence may seek certification in the Voluntary Protection Programs, subject to renewal every three to five years. While part of the program, the sites are exempt from programmed agency inspection and OSHA does not issue citations for promptly corrected violations observed during scheduled evaluations, though it still investigates complaints and other significant events. Workplaces that participate in OSHA’s program have shown significant improvements in worker safety, product quality, and profits.

A similar program in pharmaceutical manufacturing could have potentially major benefits without significant regulatory burdens.

4. Altered regulatory timelines

Rather than relying solely on procedural or substantive reforms, FDA could blend the two to change firms’ internal development incentives by requiring significantly greater understanding of drug manufacturing parameters earlier in the development process. Currently, Phase I clinical trials can begin in humans with significantly less stringent requirements for cGMP and Chemistry and Manufacturing Controls (CMC) than those required for Phase II or III trials or commercial sale. What this means in

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276 See supra Section II.A.3.a.
278 Id.
279 Brian Bennett & Norman Deitch, OSHA’s VPP The Value of Participating, 52 PROFESSIONAL SAFETY, 27, 29 (2007)
280 IND drugs are still required to comply with § 501(a)(2)(B) of the FDCA (21 U.S.C. § 351(a)(2)(B)), which mandates the use of current good manufacturing practices. However, under 21 C.F.R. § 210.2(c), drugs used in Phase I clinical trials need not conform to 21 C.F.R. § 211 (governing GMPs), unless the drug is also being used in Phase II or
practice is that firms can put off developing sophisticated knowledge of a drug’s manufacturing characteristics—how the drug can best be formulated, what inactive ingredients are most appropriate for final dosage forms, and how fast the drugs should dissolve, among others—until clinical trials have already begun. The actual requirements for CMC and cGMP information required when beginning Phase I trials are quite low because FDA is focused on guaranteeing safety, but not on other aspects of the drug’s eventual development process like the potential for high-quality manufacturing at commercial scale.\textsuperscript{281}

If FDA instead required that companies submit significant CMC and cGMP information with an IND—rather than just evidence of safety and some basic manufacturing controls—firms would be forced to generate such additional information before beginning human trials. This would help avoid the current process of locking in inefficient manufacturing processes and supply chain dynamics by establishing them, and generating the critical drug attributes that are consistently reproduced through the drug’s lifespan, during clinical trials and before investment in understanding drug manufacturing characteristics.\textsuperscript{282}

One challenge to this approach is that because the vast majority of drugs never make it to market, spending the time and money to develop information about manufacturability earlier would result in wasted investment for those drugs which will never be marketed. There are two responses to this concern which help lessen it. First, although the total development attrition rate is very high, the relevant attrition rate for this regulatory shift is from entry into Phase I trials, for which an IND is required but relatively little manufacturing understanding is required, into Phase II trials, during which manufacturing information is fully developed and where cGMP regulations come into force. Approximately 60\% of drugs which enter Phase I trials make it to Phase II trials.\textsuperscript{283} Thus, assuming that the information needs to be generated for drugs in Phase II, only 40\% of information development costs will be for drugs which Phase III trials or has been marketed. See U.S. FDA, \textit{Guidance for Industry: CGMP for Phase I Investigational Drugs}, July 2008, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf ("Phase I CGMP Guidance").

\textsuperscript{281} Conversation with Hedley Rees, Managing Consultant at PharmaFlow Consulting, March 3, 2013. See also \textit{Phase I CGMP Guidance} at 12 ("The manufacturer should establish acceptance criteria for specified attributes on each material. For some materials, all relevant attributes or acceptance criteria may not be known at the phase I stage of product development.").

\textsuperscript{282} REES, \textit{supra} note 113, at 405–07

\textsuperscript{283} Kola & Landis, \textit{supra} note 145, at 713.
ultimately fail: a high fraction, but less than half.\textsuperscript{284}

Second—and mediating the first—at least some attrition in the drug pipeline occurs for concerns related to manufacturing: in 2000, roughly 5\% of drugs failed to proceed because they were too difficult to formulate, and roughly 10\% because they were too expensive to manufacture.\textsuperscript{285} Because later phases of clinical development are significantly more expensive,\textsuperscript{286} determining earlier that a drug will be too costly to manufacture or too difficult to formulate can reduce costs later in the pipeline, partially offsetting the costs of generating unnecessary information for eventually unsuitable candidates.\textsuperscript{287}

This regulatory shift would mean that more manufacturing processes would be established on the basis of better information earlier in the drug development pipeline. Procedural requirements could thus overcome the current financial incentives to push off manufacturing development until absolutely necessary, lessening the substantive barriers of empiricism-based consistency requirements.\textsuperscript{288}

5. A separate validation pathway

One final regulatory possibility could address the challenge of FDA’s reluctance to adopt new technologies by creating a mechanism to validate new technologies detached from the drug approval process. As discussed above, FDA has historically been reluctant to accept novel technologies, especially in the context of an NDA.\textsuperscript{289} As a result, since pre-approval delay is extremely costly, firms avoid seeking approval in NDAs

\textsuperscript{284} Twenty percent of drugs make if from Phase I to Phase III. \textit{Id.}

\textsuperscript{285} \textit{Id.}

\textsuperscript{286} \textit{Id.} at 712.

\textsuperscript{287} The obvious question arises: if this approach would already save costs, why aren’t companies adopting it? One possibility is that the offset is only partial, in which case otherwise externalized social benefits of higher-quality manufacturing would need to be weighed against increased industry costs. Another factor is that firms face strong time pressures to commercialize a drug rapidly to maximize the period of patent-protected market exclusivity. Since the patent clock starts running early in development, firms may avoid generating additional manufacturing-related information before beginning human trials. The competitive features of this problem would be avoided if applied equally to all firms. If, on the other hand, requiring such a delay makes commercialization impracticable (by, for instance, unacceptably shortening the usable patent term), a patent-term extension could counterbalance the regulation-based delay.

\textsuperscript{288} See supra Section II.A.3.b. This approach could also help lessen the problem of mismatches in patent timing described earlier in note 174; if understanding and innovation shift earlier in the drug development process, more of the lifetime of any resultant patents would occur during the patent-protected period when the innovator manufacturer controls the entire market.

\textsuperscript{289} See supra Section II.A.1.
for novel manufacturing methods.\textsuperscript{290} This disincentive for manufacturing innovation can be reduced by allowing firms to introduce and validate novel techniques for FDA separate from any particular NDA.\textsuperscript{291}

If firms can demonstrate to FDA that novel manufacturing techniques function reproducibly and can be validated, that demonstration could be relied upon by FDA in any NDA or sNDA seeking to use the new technique. This would be particularly useful for broadly applicable techniques, like HPLC\textsuperscript{292} or, more currently, continuous manufacturing dynamically modulated by in-line measurements.\textsuperscript{293} Regulatory approval of a new technique could allay worries about including that technique in an NDA. Today, HPLC is used in essentially all NDAs, but it took a long time, and unusually persistent sponsors, to achieve that result. An independent process for new technologies could speed and regularize that process. It could also shield FDA reviewers from risk-averse pressures to avoid novel techniques by decoupling them from the risks of new drugs.\textsuperscript{294}

Such a standalone validation process would also ideally be open to firms other than drug sponsors; contract manufacturing organizations (CMOs), equipment vendors, and manufacturers from other industries could seek validation of relevant techniques. The incentive for this regulatory effort would vary by sponsor: efficiency and quality gains from the new technology, for a drug sponsor; potential equipment sales, for a vendor; potential clients, for a CMO; or patent royalties, for any of the above but especially manufacturers from other industries. Patent royalties or other manufacturing exclusivity incentives would provide even better incentives if the intellectual property regime for manufacturing could be improved; the next section describes such possibilities.

\textsuperscript{290} This problem exists principally for pre-approval innovation which would be incorporated into an NDA, since pre-approval delay cuts into patent-protected market exclusivity, where post-approval delays in implementing manufacturing innovations do not. However, restrictions on innovation pre-approval also limit the available possibilities for innovation post-approval through the procedural and substantive hurdles discussed in Section II.A.2.

\textsuperscript{291} See Winskill Testimony, supra note 107 at 147–48 (discussing making “dummy” submissions of new technologies, including standard operating procedures, to FDA unlinked to any particular NDA to avoid risk of regulatory delay).

\textsuperscript{292} See Section II.A.1, supra.


\textsuperscript{294} See CARPENTER, supra note 98, at 67–68.
B. Using regulation to change innovation incentives

While lowering regulatory barriers can make it easier to innovate, incentives are likely needed to drive optimal innovation past remaining barriers not present in other industries’ manufacturing sectors. Wide-reaching changes to the intellectual property system as a whole are both beyond the scope of this piece and unnecessary to address the industry-constrained problem of pharmaceutical manufacturing. However, the pervasive regulatory oversight in the pharmaceutical industry, and the successful integration of regulation with patent incentives in drug discovery, suggest that regulatory structures can help improve intellectual property incentives for innovation.

The drug industry is virtually unique in the close supervision of whether and how a product can be introduced. The costs of this supervision are large, but deemed worth it. Treating this industry oversight as a given, we can with relatively small changes and additional costs implement structural changes with potentially tremendous benefits for innovation. These structural improvements could come in two major forms. First, regulatory action could augment and change the functioning of the intellectual property system, using disclosure requirements to drive the industry from an opaque, trade secrecy-based system to a more transparent, patent-based system. Second, an expansion of regulatory market exclusivity incentives for manufacturing innovation could parallel the existing intellectual property systems, much as regulatory exclusivity for drugs already parallels the patent system.

295 It is also possible that regulatory reform alone might be sufficient. Market forces and industry dynamics will drive some innovative shifts; some studies have suggested that QbD adoption has been partially driven by business factors. See, e.g., JUNKER, supra note 267; FUHR & GEORGE, supra note 267. However, innovation theory suggests that well-functioning innovation incentives are still necessary, because firms’ inability to capture large portions of total innovation value results in underinvestment in innovation from a social perspective. See K. J. Arrow, Economic Welfare and the Allocation of Resources for Invention” in RR Nelson (ed.), The Rate and Direction of Inventive Activity. Princeton, Princeton University Press, 619 (1962); Charles I. Jones & John C. Williams, Measuring the Social Return to R&D, 113 Q.J. ECON. 1119, 1134 (1998). This is likely particularly true for manufacturing innovation in the pharmaceutical industry, since consumers are relatively cost-insensitive and thus manufacturing costs can be passed on. Quality-increasing innovation may be extremely valuable socially but relatively low value to manufacturers beyond the quality needed for regulatory approval of market entry, since that additional quality is typically opaque to consumers. See infra Section III.C. Incentives are therefore likely a necessary addition to regulatory improvements to drive socially preferable levels of manufacturing innovation.
1. Mandatory disclosure to reshape intellectual property incentives

The major misalignment of intellectual property protection for pharmaceutical manufacturing is the dominance of trade secrets over patents, driven by the widespread and accurate perception that manufacturing patents are very difficult to enforce successfully.\textsuperscript{296} Trade secrets and patents on manufacturing methods are both difficult to enforce once the competitor is using the protected process, but trade secrets can keep competitors from getting the information in the first place. If manufacturing patents were easier to observe and enforce, firms could more easily rely on them to protect their innovation investments. This swap would trade a typically shorter monopoly period (since trade secrets can exist indefinitely) for easier enforcement upon observation of infringement,\textsuperscript{297} the possibility of greater damages on a finding of willful infringement,\textsuperscript{298} and an environment of easier cumulative innovation, both in-firm and cross-firm.\textsuperscript{299} Increasing these incentives, and allowing easier cumulative innovation, could help increase the efficiency and quality of pharmaceutical manufacturing. In addition, additional industry benefits might arise from greater potential mobility of employees unburdened by nondisclosure agreements and consequent knowledge spillovers.\textsuperscript{300} Benefits to those outside the industry would include increased disclosure of whatever manufacturing innovations are generated, the possibility of greater manufacturing transparency, and the societal benefits of increased cumulative innovation.\textsuperscript{301}

Fully addressing the mechanics of this larger cultural and intellectual property regime shift is beyond the scope of this work. In brief, however, manufacturing practices would have to be significantly more

\textsuperscript{296} See supra Section II.B.1.
\textsuperscript{297} Proving appropriation of trade secrets in court is very challenging, including proving that secrets were adequately protected and that appropriation occurred instead of independent invention. See Gene Rzuclidlo & Stefan Miller, Aggressive Intellectual Property Strategies, BEST PRACTICES IN BIOTECHNOLOGY BUSINESS DEVELOPMENT: VALUATION, LICENSING, CASH FLOW, PHARMACOECONOMICS, MARKET SELECTION, COMMUNICATION, AND INTELLECTUAL PROPERTY 61, 65 (2008).
\textsuperscript{298} 35 U.S.C. § 284.
\textsuperscript{299} See, e.g., Scotchmer, supra note 156; Erkal, supra note 238; see also supra Section II.B.3.c.
\textsuperscript{301} On the flip side, an increase in patenting could potentially stifle some other forms of innovation which are currently developed in parallel but are not blocked by patent concerns, since independent invention is a defense against trade secret misappropriation actions but not patent infringement actions.
transparent so that patent infringement could be detected and the patent subsequently enforced. Such transparency would demand a significant cultural shift in an industry currently dominated by secrecy, but could be significantly facilitated by the industry’s heavily regulated nature. Manufacturers must already notify FDA of the details of their manufacturing procedures, and are subject to FDA inspections. While actually enforcing manufacturing patents is well outside the scope of FDA’s authority, making publically available the registered manufacturing techniques and other manufacturing information currently maintained confidentially by FDA would allow firms to police their patented techniques themselves. Such an approach would not be easy; in particular, there are significant statutory and potentially constitutional problems with revealing information previously disclosed to FDA as confidential.\footnote{Richard A. Epstein, The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009, 66 FOOD & DRUG L.J. 285 (2011).} As a prospective solution for NDAs, ANDAs, and other manufacturing changes going forward, however, this idea faces fewer challenges.

In fact, Congress has already mandated a limited version of this approach in the approval process for biosimilars as authorized by the Biologics Competition and Innovation Act of 2009 (BCPIA).\footnote{Pub. L. No. 111-148, 124 Stat. 119, §§ 7001–03.} The BCPIA created an abbreviated approval pathway for biosimilars, but within 20 days of FDA’s acceptance of an application for a biosimilar, the biosimilar applicant must provide a copy of the application to the reference product sponsor, including the method by which the biosimilar is manufactured.\footnote{42 U.S.C. § 262(l)(2)(A).} This information may only be viewed by the reference product sponsor’s counsel, may not be disclosed to other employees, and can be used only to determine potential patent infringement.\footnote{42 U.S.C. §§ 262(l)(B)-(D). Unlike small-molecule drugs, for which patents are centrally registered in the Orange Book, patents on biologics are not registered. The BPCIA thus sets up a complex scheme in which the pioneer and follow-on manufacturers exchange information on relevant patents. 42 U.S.C. § 262(l). See Dougherty, supra note 172.} This method of enforcing manufacturing patents is unlinked to the FDA’s safety and efficacy mandate; instead, the FDA approval process facilitates enforcement of manufacturing patents by requiring disclosure to the most relevant patent-holder.\footnote{This process creates an advantage for the reference product sponsor as against any other holder of potentially relevant manufacturing process patents, which still face the standard difficulties enforcing their patents.} In at least this context, transparency is already required to facilitate patent protection and enforcement.
Changing from opacity to transparency would be a major shift for industry. However, more complex new technologies will are required to manage and evaluate production, especially for biologics. Broad and cumulative innovation could well be worth the costs of mandated transparency.


Rather than trying to shift the industry from a trade-secrecy regime to a patent-based regime for manufacturing innovation, FDA could administer a parallel set of market protection incentives which could be more carefully tailored to industry dynamics than patent or trade-secrecy regimes. Currently, FDA market protection is statutorily available only for innovation in drug discovery or development; this regime could be Congressionally expanded to include innovation in manufacturing. This parallel system could grant market protection, in the form of statutory market exclusivity, either to the manufacturing innovation itself or to a related or unrelated drug.

To address the less intuitive but more familiar solution first, FDA could reward manufacturing innovations by granting an additional period of market exclusivity to a drug. The most straightforward form of this exclusivity would be granting market exclusivity to the drug product for which the manufacturing innovation was designed. If, for instance, Pfizer discovered an innovative new way to manufacture higher-quality Lipitor, FDA could extend Pfizer’s regulatory exclusivity on Lipitor by keeping generic Lipitor off the market for an additional period of time. This is the approach taken with pediatric clinical trials; a firm completing pediatric trials receives an additional six months of market exclusivity.307 Such a linked approach would be harder to apply to manufacturing innovations which are not linked to a specific drug, like an improved technique for ensuring tablet uniformity. That problem could be avoided by granting so-called “wild-card” extensions, which would allow the firm to apply regulatory exclusivity to any drug in its portfolio; such wild-card extensions have been previously suggested as regulatory prizes for different types of pharmaceutical innovation.308

There are significant concerns with product-based regulatory exclusivity, centered on appropriately valuing the innovation. FDA might have difficulty determining whether a manufacturing innovation is significant enough to merit the bonus of regulatory exclusivity. In addition,

307 See supra note 195 and accompanying text.
FDA would need some mechanism of screening out useful innovations from marginal or inefficient innovations to avoid a situation of drug exclusivity continually extended by small manufacturing changes. The appropriate length for such an extension would also be difficult to determine, though for most drugs, even a very short extension might be enough to overcome the hurdles currently hindering innovation. Furthermore, the value of the incentive may differ significantly by company, because the value of a fixed period of time depends on the market value of the drug; firms with higher-selling drugs would receive more value from the same period of exclusivity.\textsuperscript{309} These difficulties make product-based regulatory exclusivity a problematic form of innovation incentive.

Alternately, regulatory exclusivity could be granted to the manufacturing innovation itself, by preventing other firms from using the innovation for some period of time. Major manufacturing changes already require FDA approval to implement. Thus, if a company demonstrated an innovative and useful major change in manufacturing and FDA approved it for that company, FDA could register the change and explicitly refuse to approve other companies’ implementation of that change for a period of time.\textsuperscript{310} Once the exclusivity period expired, all pending manufacturing change applications to use the innovative process would be approved.

Applying regulatory exclusivity to efficiency-based innovations seems relatively unproblematic, though those innovations are most likely to be pursued as worthwhile even without outside incentives. Creating exclusivity for quality-improving manufacturing innovation is initially harder to square with FDA’s mission of ensuring high drug quality. If a manufacturing process increases the quality of a final drug product, it seems highly counterintuitive for FDA to then prevent other manufacturers from using the same procedure. However, in other contexts FDA similarly prioritizes innovation incentives. For instance, pediatric studies are rewarded with exclusivity for the entire drug line, for all uses, not just

\textsuperscript{309} Getting value from regulatory exclusivity also requires having drugs where regulatory exclusivity would keep competitors off the market; firms whose drugs have strong and ongoing patent protection which would overlap the period of regulatory exclusivity would receive less benefit from the exclusivity than firms without patent protection.

\textsuperscript{310} It is an arguable question—and one outside the scope of this article—whether FDA could implement such a significant policy absent statutory authorization. At least in theory, the approval of manufacturing changes is left to the discretion of the agency, and encouraging manufacturing innovation is at least a plausible justification for delaying major manufacturing changes. On the other hand, such a justification is certainly a major step away from the traditional safety-based justifications for regulatory approval of manufacturing changes, and market protection for drugs has relied on Congressional action.
pediatric uses; this sacrifices access to a drug for the sake of more information for pediatric users.\textsuperscript{311} In the long run, innovation is judged to be worth the short-term sacrifice.

Regulatory exclusivity for manufacturing innovation would avoid one of the key problems of manufacturing process patents: the difficulty of enforcement. Since FDA oversees pharmaceutical manufacturing, requires registration of manufacturing techniques, and pre-approves major changes in manufacturing, the agency could readily prevent a firm from using a technique for which regulatory exclusivity had been granted.

Regulatory exclusivity would not, however, avoid another major reason that actual patents—as opposed to regulatory “pseudo-patents”—fail to create adequate incentives for manufacturing innovation: the problem of public disclosure to competitors. If manufacturing innovations require public disclosure to receive FDA regulatory exclusivity, firms might avoid seeking that exclusivity to avoid that disclosure, a key reason patents already ineffective. If FDA exclusivity occurs without public disclosure, on the other hand, the social and industrial benefits of that disclosure are lost.

Institutional competence is a much larger challenge. Applying regulatory exclusivity to manufacturing innovation would substantially extend the “pseudo-patent” regime beyond the very discrete world of drug products and yes-or-no activities like the completion of pediatric trials or the approval of a new indication. It would demand that the agency make hard judgments about what innovation is enough to justify exclusivity, what the boundaries of an innovation are, what happens when two companies both seem to develop an innovation simultaneously, and what do to if one innovation incorporates another. These issues are all familiar ones, but are familiar in the context of patent law, where firms can rely on the expertise of the PTO and a large body of law developed by the federal courts. FDA currently lacks the institutional competence, and the mandate, to develop a truly parallel pseudo-patent system alongside the actual patent regime.

Overall, while market exclusivity is the traditional form of incentive for innovation, using either form of government-based exclusivity—patent or regulatory—is challenging for manufacturing innovations. Shifting from a secrecy-based system of manufacturing innovation to a patent-based system is an intriguing and promising possibility, but demands systematic changes in transparency throughout the industry. Regulatory exclusivity seems a more straightforward fix, which has been applied before when incentives were needed for pharmaceutical companies, but applying such innovations to manufacturing innovation raises particularly challenging questions of valuation and institutional competence.

C. Quality indicators and market pressure

Firm behavior is typically driven by market demand. However, with respect to manufacturing quality, the market is effectively unable recognize or reward drug quality; thus, the market does not demand a particular quality of product.\(^\text{312}\) Dr. Janet Woodcock, Director of CDER, recently noted this in the context of drug shortages, specifically shortages of generic sterile injectables.\(^\text{313}\) A key reason for those shortages is that healthcare consumers (whether doctors, hospitals, or the group purchasing organizations which act as middlemen in many drug markets) are unable to discern differences in quality between products of different manufacturers.\(^\text{314}\) Because all generic versions of a drug are designed—and are required—to have “the same efficacy and side effect profiles,” buyers consider the drugs to be perfect substitutes, and assume that “the products are of sufficient quality if they are on the market.”\(^\text{315}\) Accordingly, manufacturers compete only on price, not on quality, resulting in non-robust manufacturing procedures prone to breakdowns and causing shortages.\(^\text{316}\)

This lack of quality competition is hard for consumers, insurers, and FDA itself to detect. Microbial contamination, in particular, can be episodic and non-uniform; a poorly maintained or designed production line may only intermittently introduce contamination, which may itself be relatively benign or very harmful.\(^\text{317}\) Thus, traditional after-the-fact sampling protocols performed by the manufacturer and reviewed by FDA

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\(^{312}\) Woodcock & Wosinska, supra note 44.

\(^{313}\) Id. at 171.

\(^{314}\) Id.

\(^{315}\) Id. In addition, in the specific markets analyzed by Dr. Woodcock, quality may be especially difficult to measure after the fact. In many markets, even if there is no \textit{ex ante} way for consumers to differentiate products based on quality, products can be differentiated \textit{ex post} based on product performance and the rate of product failure. Sterile injectable and infusible drugs, however, are usually administered to patients with compromised immune systems and lack the ability to effectively fight infections. Id. at 172. Accordingly, drug contamination events are difficult to differentiate from infections which might otherwise occur in the treated population. Id. Most healthcare providers do not look to manufacturing products when they observe infections in, for instance, the cancer patients treated with a chemotherapy regime of (assumed-to-be) sterile injectable drugs, assuming—correctly—that such manufacturing defects are relatively rare and that infections from other sources are relatively common. Id. Accordingly, few providers will make the causal link and report that an adverse event is based on manufacturing problems.

\(^{316}\) Id.

\(^{317}\) Id. Other forms of contamination beside the microbial may also occur only in some instances, such as the presence of glass or metal shards in product vials. Id. at 171.
may miss sources of contamination. Contributing to the lack of regulatory incentives for maintaining the highest quality standards, FDA’s response to contamination events is frequently tempered by its desire to avoid drug shortages. Thus, manufacturers face both a market which is approximately indifferent to quality because quality is hard to observe, and a regulatory structure which can only sometimes detect quality problems and which imposes a restrained response to problems once they are detected.

As a result of this market and regulatory insensitivity to quality, “short-sighted firms [have] an incentive to manufacture under a minimum level of control.” Many manufacturers therefore “minimize quality system investments.”

To cope with the lack of quality awareness, particularly in the market, Dr. Woodcock suggests that “FDA could support buyers and payers in their purchase and reimbursement decisions by providing them with meaningful manufacturing quality metrics.” Such metrics would be analogous to the use of scorecards for Health Management Organizations (HMOs), or grades given to restaurants by health inspectors. They would demonstrate quality above that required by cGMP regulations.

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318 Woodcock & Wosinska, supra note 44, at 172.
319 Id.
320 Id.
321 Id. at 173.
322 Id. at 175. Dr. Woodcock did note that a few firms “strive to exceed minimum manufacturing standards.” Id. at 172. Part of the difference may be driven by firm reputation; other differences may be driven by more straightforward economic factors. Branded sterile injectable manufacturers were twenty times as likely as generic sterile injectable manufacturers to reference a backup facility for drug production when submitting an ANDA (20% vs. 1%). Id. at 174–75. Branded drugs have far higher profit margins than generic drugs, such that the threat of lost sales is far more significant for branded manufacturers than generic manufacturers; accordingly higher investments in plant redundancy are expected.
323 Woodcock & Wosinska, supra note 44, at 175.
324 In California, the state provides quality ratings for health insurance plans, including HMOs, as well as for health care providers. “Health Care Quality Report Card,” California Office of the Patient Advocate, http://opa.ca.gov/report_card/ (last visited February 13, 2013).
326 As FDA’s cGMP standards are defined, at least technically, as a set of requirements, any violation of which results in a drug’s being adulterated and subject to enforcement. FDA-backed quality standards would therefore have to assume a baseline of fulfilling cGMP regulations. Examples of quality criteria surpassing cGMP requirements might include additional rounds of sterilization, significantly lower active ingredient variability than the +/- 10% range typically permitted by FDA, continuous process
FDA is currently planning to create a drug quality program implemented by a newly instituted Office of Pharmaceutical Quality within CDER.\textsuperscript{327}

While this idea has significant potential, it might have limited effects on manufacturing innovation. Even regulator-enforced quality grades might not be transparent to the consumer. As in many aspects of healthcare, the question of who exactly constitutes the market-oriented consumer is nontrivial. In retail settings, consumers might pay a premium for drugs with a prominent signal of high-quality manufacturing and avoid those with a low-quality signal, changing market incentives. However, institutional purchasers—who dominate the market for many drugs with the most prevalent manufacturing quality issues—may not be concerned about minor differences in quality as long as the firm has met FDA’s marketability threshold. Since FDA certification provides a basic quality guarantee, liability would be unlikely to result from failing to pay a premium for additional manufacturing quality.\textsuperscript{328} This institutional lack of participation is especially likely to be true if quality metrics are not transparent to the final consumers. If patients, as now, are given drugs removed from their initial packaging and dispensed through a hospital’s pharmacy system the quality signals present in retail packaging would be absent at the time of use. Therefore, institutions could freely prioritize lower cost over paying a quality premium.

This approach could be modified to give greater industry incentives by leveraging the dynamic between brand and generic companies. If, in the drug approval process, a firm could commit to higher quality standards—say, a $\pm$ 1% variation in active ingredient, rather than the typically permitted $\pm$ 10%—that commitment could be added to the label and thus become enforceable by FDA. As a natural consequence, any firm seeking approval to market a generic version of the drug would have to match that commitment, and meet the same quality standard. This would allow firms to erect a quality barrier to generic entry. Previous work has shown that fewer generics compete for hard-to-manufacture formulations.\textsuperscript{329} This approach creates incentives for both branded and generic manufacturers to increase manufacturing quality, without relying on consumer or insurer preferences to generate those incentives. To limit generic entry, branded-drug makers would need to invest in higher-quality manufacturing, while generic companies, to avoid exclusion from the market, would need to

\textsuperscript{327} Hamburg, supra note 80.

\textsuperscript{328} As noted before, tort preemption is a particularly tangled doctrine at the moment, and may change. See supra note 247.

invest as well. Consumers would receive higher quality drugs, both from the brand company and from any compliant generics. This benefit would, of course, need to be measured against potentially higher generic prices from decreased or delayed generic entry.

CONCLUSION

This article has argued that studies of innovation policy in the pharmaceutical industry, both at the policy level and in the academy, have until now missed a crucial piece of the industry puzzle: the costs and complexities of pharmaceutical manufacturing. This gap in theory, which this article seeks to remedy, has had major practical consequences. A combination of regulatory policy with both several barriers to manufacturing innovation and an intellectual property regime poorly aligned to incentives for manufacturing innovation results in tens to hundreds of billions of dollars in lost social economic welfare, in addition to major human costs from drug shortages and recalls.

This article identifies as the principal cause of these problems a gap in innovation theory and policy, particularly in the pharmaceutical industry but also more generally, regarding the role of innovation in manufacturing processes. New products must be made and distributed for society to receive their benefit. While it is typically assumed that manufacturing and distribution will be straightforward, the case of the pharmaceutical industry demonstrates that is not always true. When regulation and incentives actively hinder manufacturing innovation, that hindrance can have profoundly problematic consequences. Legal rules that work to drive innovative product development may not work for manufacturing—and for drug manufacturing, a single example but one of tremendous importance to the economy and to public health, those rules significantly slow innovation.

However, this policy gap regarding different forms of innovation is amenable to new solutions in the form of regulatory shifts. Discovery and development of new drugs is a paradigm area where regulation is actively shaped to encourage innovation; manufacturing those drugs is another area for regulation to press forward. A parallel system of intellectual property incentives, or more drastic changes shifting the way already existing incentives function in the industry, are two major possibilities, but other options may be proposed once the role of regulation in directly managing innovation is more fully appreciated. Such approaches are not limited to the pharmaceutical industry, though they may now be palatable or even conceivable only in that industry given its unusually heavily regulated nature. Thus, these methods suggest new ways of using regulatory levers for innovation in other contexts, especially substantively related industries.
with tight regulation, such like medical devices or biomedical diagnostics. There is an ongoing debate over the role of different intellectual property forms in balancing initial innovation investments against restrictions on following innovation. In this context, the possibilities of altering which intellectual property form dominates in a particular industry, or of using administrative forms to generate new innovation incentives, may have far-reaching implications.