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MAKING DO IN MAKING DRUGS: INNOVATION POLICY AND PHARMACEUTICAL MANUFACTURING

W. NICHOLSON PRICE II*

Abstract: Despite increasing recalls, contamination events, and shortages, drug companies continue to rely on outdated manufacturing plants and processes. Drug manufacturing's inefficiency and lack of innovation stand in stark contrast to drug discovery, which is the focus of a calibrated innovation policy that combines patents and FDA regulation. Pharmaceutical manufacturing lags far behind the innovative techniques found in other industries due to high regulatory barriers and ineffective intellectual property incentives. Among other challenges, although manufacturers tend to rely on trade secrecy because of the difficulty in enforcing patents on manufacturing processes, trade secrecy provides limited incentives for innovation. To increase those incentives, this Article suggests several direct regulatory reforms and proposes novel ways to use those reforms to improve innovation policy in drug manufacturing and beyond. For example, the FDA could operate a system of temporary market exclusivity for manufacturing innovation parallel to the patent system. Alternatively, the FDA could require disclosure of manufacturing methods to drive the industry from opacity and trade secrecy towards transparency and patent protection for innovation. Overall, the potentially immense economic and health benefits from more innovative manufacturing in the drug industry suggest that manufacturing may be a profitable target of innovation policy in other highly regulated industries and that manufacturing in general deserves a more prominent place in innovation policy and theory.

INTRODUCTION

M&M chocolate candies are made with a precision far beyond the capabilities of many drug manufacturers.¹ This disparity is surprising because the drug

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¹ Telephone Interview with John Helferich, Former Senior Vice President of Research & Dev., Mars/Masterfoods (May 15, 2013); Telephone Interview with Ajaz Hussain, Former Deputy Dir. of the Office of Pharm. Sci., U.S. Food & Drug Admin. (Apr. 24, 2013). Manufacturing in the drug in-

industry is tightly regulated by the U.S. Food and Drug Administration (FDA)—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.²

Drug recalls based on quality issues are one such problem. For example, in 2011, a record 2329 drug products were recalled.³ Quality issues and contamination during manufacturing or repackaging caused most of the recalls.⁴ Similarly, in 2009, two drug manufacturers recalled contaminated batches of the crucial anesthetic drug propofol, causing long-lasting shortages of the drug and one manufacturer's exit from the market.⁵ 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.⁶ The drugs did not return to the shelves for seven months.⁷ And in 2012 and 2013, fungal contamination of steroid injections made by the New England Compounding Center resulted in forty-eight deaths from fungal meningitis⁸ and hundreds of additional infections across twenty-three states.⁹

dustry has also been characterized as “far behind [that] of potato-chip and laundry-soap makers.” Leila Abboud & Scott Hensley, *New Prescription for Drug Makers: Update the Plants—After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst*, WALL ST. J., Sept. 3, 2003, at A1. Little has changed in the past decade. Agnes Shanley, *The Pulse of Pharmaceutical Manufacturing*, PHARMAMANUFACTURING.COM (Apr. 4, 2012), <http://www.pharmamanufacturing.com/articles/2012/050.html>, archived at <http://perma.cc/J38X-2U3A>.

² See *infra* notes 44–59 and accompanying text (examining the costs of drug manufacturing); *infra* notes 60–91 and accompanying text (describing the lack of innovation in the industry); *infra* notes 142–153 and accompanying text (discussing the industry's adherence to outdated manufacturing techniques out of fear of regulatory approval delay).

³ Agnes Shanley, *cGMP Judgment Day*, PHARMAMANUFACTURING.COM (Dec. 3, 2012), <http://www.pharmamanufacturing.com/articles/2012/159.html>, archived at <http://perma.cc/KN9Q-N99U>.

⁴ *Id.*

⁵ Valerie Jensen & Bob A. Rappaport, *The Reality of Drug Shortages—The Case of the Injectable Agent Propofol*, 363 NEW ENG. J. MED. 806, 806 (2010).

⁶ Eryn Brown, *Recall: Mix-up Pulls Excedrin, Bufferin, Other Meds off Shelves*, L.A. TIMES (Jan. 9, 2012), <http://articles.latimes.com/2012/jan/09/news/la-heb-novartis-excedrin-recall-painkillers-20120109>, archived at <http://perma.cc/TTF9-ZW6Z>.

⁷ Jie Jenny Zou, *Excedrin Production Resumes*, WALL ST. J. (July 26, 2012, 4:54 PM), <http://blogs.wsj.com/health/2012/07/26/excedrin-production-resumes>, archived at <http://perma.cc/FUB3-M85J>.

⁸ *Lethal Medicine Linked to Meningitis Outbreak*, 60 MINUTES (Mar. 10, 2013), http://www.cbsnews.com/8301-18560_162-57573470/lethal-medicine-linked-to-meningitis-outbreak, archived at <http://perma.cc/4SFA-S4KK>.

⁹ Jordan Paradise, *Follow-on Biologics: Implementation Challenges and Opportunities: Foreword*, 41 SETON HALL L. REV. 501, 502–03 (2011); *Lethal Medicine Linked to Meningitis Outbreak*, *supra* note 8.

Drug manufacturing problems are not limited to recalls and contamination. Over 15% of the nation's soaring healthcare costs are spent on drugs.¹⁰ And up to \$50 billion is wasted on inefficient drug manufacturing annually.¹¹ Overall, manufacturing costs comprise anywhere from 15% to over 50% of firm-level revenue.¹² 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 reinvested into research and development (R&D) to increase future health gains. Depending on how the firm uses the savings, a 20% reduction could create an annual consumer surplus worth \$47.4 billion to \$574 billion.¹³ Despite these potential benefits, firms frequently use outdated production techniques and old manufacturing plants with little innovative change to increase efficiency or quality.¹⁴

This lack of innovation in drug manufacturing is striking because the drug industry is otherwise a major and successful focus of innovation policy.¹⁵ Intellectual property and the FDA's regulatory barriers create carefully calibrated incentives for firms to discover and develop drugs.¹⁶ In addition to their independ-

¹⁰ Katie Thomas, *U.S. Drug Costs Dropped in 2012, but Rises Loom*, N.Y. TIMES, Mar. 19, 2013, at A1. Note that in 2012, drug expenditures actually dropped by around 1%. *Id.* This was due to many popular drugs' patents expiring at the same time, allowing generics to flood the market and, thus, lowering drug expenditures. *Id.* This phenomena has been designated the "patent cliff," and is not expected to continue. *Id.*

¹¹ Pradeep Suresh & Prabir K. Basu, *Improving Pharmaceutical Product Development and Manufacturing: Impact on Cost of Drug Development and Cost of Goods Sold of Pharmaceuticals*, 3 J. PHARMACEUTICAL INNOVATION 175, 186 (2008). See generally *infra* notes 92–107 and accompanying text (discussing the potential cost-saving benefits of improving manufacturing processes).

¹² See *infra* notes 44–59 and accompanying text (analyzing the differing manufacturing costs across the drug industry's three main sectors: brand-name small-molecule drugs, generic small-molecule drugs, and biologics).

¹³ J.A. Vernon et al., *Pharmaceutical Manufacturing Efficiency, Drug Prices, and Public Health: Examining the Causal Links*, 41 DRUG INFO. J. 229, 236 (2007). See generally *infra* notes 92–107 and accompanying text (discussing the potential benefits of improving manufacturing processes).

¹⁴ See *infra* notes 60–91 and accompanying text (discussing the lack of innovation in pharmaceutical manufacturing and the resulting negative effects on the drug industry).

¹⁵ See *infra* notes 223–229 and accompanying text (describing the role patents play in encouraging drug discovery); *infra* notes 270–283 and accompanying text (noting the FDA's power to grant market-exclusivity to certain drug producers and this power's role in spurring drug R&D). This Article uses the term "innovation" broadly, to include not only technological innovation, but also innovation in business practices. See generally Daniel F. Spulber, *Should Business Method Inventions Be Patentable?*, 3 J. LEGAL ANALYSIS 265, 271–75 (2011) (describing how "business method inventions" are important to economic growth). This Article also uses "innovation" to refer to the development of costly bodies of information related to and underlying other forms of innovation. See generally Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 366–72 (2007) (characterizing the FDA's innovation policy role in promoting the creation of costly information on drug safety and efficacy).

¹⁶ See *infra* notes 130–136 and accompanying text (explaining that FDA regulations induce drug discovery by creating barriers to entry that prevent competitors from entering the market); *infra* notes 205–212 and accompanying text (discussing the roles of patents and FDA regulatory exclusivity in promoting drug discovery).

ent effects, intellectual property and regulation work together because regulation not only creates hurdles to overcome, but also enhances patent incentives.¹⁷

Although the effects of innovation policy on drug discovery and development have been well studied, policy and academic debates about innovation incentives have largely ignored the important role of manufacturing innovation.¹⁸ 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.¹⁹ As a result, firms in other industries improve manufacturing and reliably provide marketable products.²⁰ 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.²¹ If manufacturing is better understood through innovation theory, then 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.²² Furthermore, the FDA approval process itself strengthens the market power of drug patents.²³ Patents on manufacturing processes, however, are very hard to enforce and do not receive a boost from the

¹⁷ See *infra* notes 130–136 and accompanying text; *infra* notes 205–212 and accompanying text.

¹⁸ For a sample of the extensive literature focusing on innovation policy on drug discovery and development, but not addressing manufacturing innovation, see generally, for example, Harvey E. Bale Jr., *Patent Protection and Pharmaceutical Innovation*, 29 N.Y.U. J. INT'L L. & POL. 95 (1996); Ron A. Bouchard et al., *The Pas de Deux of Pharmaceutical Regulation and Innovation: Who's Leading Whom*, 24 BERKELEY TECH. L.J. 1461 (2009); Brian R. Bouggy, *Follow-on Biologics Legislation: Striking a Balance Between Innovation and Affordability*, 7 IND. HEALTH L. REV. 367 (2010); Eisenberg, *supra* note 15; Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NAT. REV. DRUG DISCOVERY 479 (2008); Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MO. L. REV. 645 (2011); Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193 (2005).

¹⁹ See *infra* notes 60–62 and accompanying text (noting that the drug industry still lags in implementing modern manufacturing techniques that were developed in the 1980s and readily adopted in other industries).

²⁰ See *infra* notes 61–62 and accompanying text.

²¹ See *infra* notes 122–283 and accompanying text (outlining how intellectual property and the FDA fail to incentivize manufacturing innovation in the pharmaceutical industry).

²² See *infra* notes 223–283 and accompanying text (discussing the roles and shortcomings of patents and FDA market exclusivity in encouraging manufacturing innovation).

²³ See *infra* notes 136, 223–269 and accompanying text (discussing patents and how FDA approval requirements strengthen the exclusivity of patents).

FDA.²⁴ Firms therefore forego manufacturing patents for trade secrets. But trade secrets block cumulative innovation and may insufficiently reward some important types of manufacturing innovation.²⁵ Other industries may also face inadequate incentives for manufacturing innovation but do not face the intense regulatory barriers present in the pharmaceutical industry.

The drug industry's regulatory barriers also slow manufacturing innovation. Rather than enhancing and fine-tuning innovation incentives, FDA regulations obstruct manufacturing innovation by raising significant barriers to innovative change, both before and after drug approval.²⁶ Firms avoid introducing new technologies when seeking approval based on historically justified fears of pre-approval delay from reviewers leery of new technology.²⁷ After approval, changes to manufacturing processes face procedural hurdles that can wholly prevent continual process improvement.²⁸ 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.²⁹ 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.³⁰

Broader than any specific failure of innovation or regulation is the mismatch between the two. The classic justification for intellectual property is that it increases innovation incentives above the socially suboptimal investment baseline;³¹ this occurs against an assumed background of regulatory freedom to innovate. When intellectual property incentives are less effective, but innovation is substantially unhampered by regulation, firms can still innovate at or slightly

²⁴ See *infra* notes 226–240 and accompanying text (noting the difficulties of enforcing process patents); *infra* notes 270–283 and accompanying text (explaining that, unlike drug discoveries, FDA regulations do not create market exclusivity for manufacturing innovations).

²⁵ See *infra* notes 284–331 and accompanying text (analyzing trade secret's role and shortcomings in promoting manufacturing innovation).

²⁶ See *infra* notes 130–204 and accompanying text (explaining how FDA regulations create hurdles to manufacturing innovation in the pharmaceutical industry).

²⁷ See *infra* notes 142–154 and accompanying text (discussing preapproval barriers for new drug applications and describing the FDA's resistance to accepting a new manufacturing technique: high performance liquid chromatography ("HPLC")).

²⁸ See *infra* notes 171–183 and accompanying text (discussing postapproval filing requirements for major, moderate, and minor process changes).

²⁹ See *infra* notes 184–204 and accompanying text (discussing postapproval FDA regulatory lock-in).

³⁰ See *infra* notes 155–167 and accompanying text (providing an example of the industry's pervasive blind adherence to FDA examples by describing the development of the industry's three-batch standard for certain tests resulting from the FDA's use of three batches in a guidance document).

³¹ Suzanne Scotchmer, *Standing on the Shoulders of Giants: Cumulative Research and the Patent Law*, 5 J. ECON. PERSP. 29, 30–31 (1991); see *infra* notes 223–269 and accompanying text (discussing patent structure and why patents fail to incentivize manufacturing innovation in the pharmaceutical industry).

above that baseline. This is the case with manufacturing methods in many industries. And when regulatory restrictions are intense and costly, but policy rewards are high, firms still innovate because policy-driven benefits of innovation exceed the costs. This is the case with the development of new drugs because development requires costly clinical trials, but receives effective patent protection and regulatory market exclusivity. But when regulatory burdens to innovation are high *and* exclusivity incentives are weak and ineffective, the net motivation to innovate is low. This is the case with drug manufacturing.

As a result of ineffective innovation policy, drug manufacturing has been close to stagnant for decades, lagging far behind the innovative manufacturing advances of other industries. Even the regulatory standards now imposed reflect a poorly controlled state of manufacturing. For instance, the amount of an active ingredient in a drug can typically vary by as much as $\pm 10\%$, so the difference between two approved tablets in the same bottle could be as much as 20% .³²

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 be to lessen current regulatory barriers to innovation to the extent possible while letting the 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, the FDA could deliberately shape innovation incentives. The effect of regulation on innovation has been studied before,³³ but previous studies have paid much less attention to the way regulation could be used as a policy lever to actively drive innovation by changing incentives.³⁴ The FDA administers incentives for drug discovery and development already.³⁵ This Article suggests two possible approaches to expand and flexibly apply the FDA's incentive-shaping approach to manufacturing innovation. First, a system of FDA-mediated market exclusivity, parallel to that for drug approval, could be institut-

³² See U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: INVESTIGATING OUT-OF-SPECIFICATION (OOS) TEST RESULTS FOR PHARMACEUTICAL PRODUCTION 10 (2006), *available at* <http://www.fda.gov/downloads/Drugs/Guidances/ucm070287.pdf>, *archived at* <http://perma.cc/JC4-6NJ4>.

³³ This literature is especially extensive in the area of environmental regulation. See generally, 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 CALIF. L. REV. 1256 (1981); Margaret R. Taylor et al., *Regulation as the Mother of Innovation: The Case of SO₂ Control*, 27 L. & POL'Y 348 (2005).

³⁴ A few articles have been written in the context of the FDA and drug discovery. See generally, e.g., Eisenberg, *supra* note 15; William E. Ridgway, Note, *Realizing Two-Tiered Innovation Policy Through Drug Regulation*, 58 STAN. L. REV. 1221 (2006).

³⁵ Eisenberg, *supra* note 15, at 359–64, 366–72.

ed. Alternatively, the 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.³⁶ Part II then describes the regulatory and intellectual property reasons for manufacturing stagnation.³⁷ Finally, Part III suggests potential regulatory solutions to increase innovation, including both pure regulatory and incentive-shifting possibilities.³⁸

I. THE STATE OF PHARMACEUTICAL MANUFACTURING

Manufacturing is either the largest or second-largest expense for pharmaceutical firms.³⁹ 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.”⁴⁰ 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.

Section A of this Part discusses the high costs of manufacturing across the industry’s three main segments.⁴¹ Section B analyzes the various causes and effects of the industry’s current lack of manufacturing innovation.⁴² Finally, Section C discusses the potential benefits from updating manufacturing processes, including reduced costs and improved quality.⁴³

³⁶ See *infra* notes 39–121 and accompanying text.

³⁷ See *infra* notes 122–331 and accompanying text.

³⁸ See *infra* notes 332–444 and accompanying text.

³⁹ Prabir Basu et al., *Analysis of Manufacturing Costs in Pharmaceutical Companies*, 3 J. PHARMACEUTICAL INNOVATION 30, 33 fig.1 (2008); see *infra* notes 44–59 and accompanying text (discussing manufacturing costs). For brand-name and biologics companies, sales and marketing are generally the highest costs, and for generics, manufacturing is by far the largest cost. See *infra* notes 44–59 and accompanying text.

⁴⁰ Joanne Eglavitch, *Regulatory Relief Explored for QbD Use in Post-Approval Changes*, GOLD SHEET (Aug. 30, 2012, 12:00 AM), available at <http://www.elsevierbi.com/publications/the-gold-sheet/46/8/regulatory-relief-explored-for-qb-d-use-in-postapproval-changes> (quoting Moheb Nasr, Vice President of Regulatory Chemistry and Manufacturing Controls Strategy for GlaxoSmithKline and former Director at the FDA’s Office of New Drug Quality Assessment).

⁴¹ See *infra* notes 44–59 and accompanying text.

⁴² See *infra* notes 60–91 and accompanying text.

⁴³ See *infra* notes 92–121 and accompanying text.

A. High Costs of Manufacturing Across the Pharmaceutical Industry

Widespread misperceptions that drug manufacturing is very inexpensive⁴⁴ arise from a focus on marginal costs.⁴⁵ Marginal costs are frequently very low, especially for blockbuster small-molecule drugs.⁴⁶ Other drugs, however, typically have higher marginal costs.⁴⁷ Furthermore, the industry as a whole 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 companies’ costs.⁴⁸

Manufacturing costs differ across the drug industry’s three 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, COGS were approximately 26% of sales between 1994 and 2006.⁴⁹ Generics spent more on manufacturing, averag-

⁴⁴ See Jennifer S. Bard, *What to Do When You Can’t Hear the Whistleblowing: A Proposal to Protect the Public’s Health by Providing Whistleblower Protection for Medical Researchers*, 9 IND. HEALTH L. REV. 1, 34 (2012) (noting that “once a drug is developed, it costs very little to manufacture”); Irwin I. Park, *Extinguishing Exclusive Marketing Rights: Interpreting the Medical Innovation Prize Fund Act of 2011*, 22 DEPAUL J. ART TECH. & INTELL. PROP. L. 183, 214 n.217 (2011) (arguing that drug innovation prizes could increase profits, “assuming that manufacturing costs are minimal”).

⁴⁵ Marginal costs measure the cost of manufacturing one extra pill. Cf. J. Gregory Sidak & Daniel F. Spulber, *Deregulatory Takings and Breach of the Regulatory Contract*, 71 N.Y.U. L. REV. 851, 868 n.43 (1996) (defining “marginal cost”). For example, marginal cost is the price of going from the one-millionth pill to the one-million-and-first pill. Cf. *id.* Fixed and marginal production costs vary by drug, and precise production costs are generally unavailable. Ernst R. Berndt et al., *Information, Marketing, and Pricing in the U.S. Antiulcer Drug Market*, 85 AM. ECON. REV. 100, 100 (1995).

⁴⁶ See Outterson, *supra* note 18, at 253 (noting that although most drug manufacturers do not disclose patented drugs’ marginal manufacturing costs, differential pricing ratios can be used as a proxy: “[They] currently exceed 30:1 in [anti-retroviral] drugs, implying marginal costs of production in the range of 3 to 4%.”).

⁴⁷ See Berndt et al., *supra* note 45, at 100 (suggesting that for one group of anti-ulcer drugs, marginal production costs ranged from 10–25% of the drugs’ price).

⁴⁸ See *infra* notes 49–59 and accompanying text (explaining the various COGS of different industry segments and noting that COGS can account for over half of some firms’ revenues).

⁴⁹ Basu et al., *supra* note 39, at 33 fig.1; see also Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLOS MED. 29, 29–30 (2008), available at <http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.0050001&representation=PDF>, archived at <http://perma.cc/8KA6-M66F> (reporting that, according to one study, ten of the largest global pharmaceutical firms spent 30% of total revenue on COGS and 12% on R&D between 1996 and 2005). Large drug companies’ annual reports support these survey-based conclusions. See, e.g., GLAXOSMITHKLINE, DO MORE, FEEL BETTER, LIVE LONGER: ANNUAL REPORT FOR SHAREHOLDERS 136–37 (2011), <http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-Annual-Report-2011.pdf>, archived at <http://perma.cc/VBZ9-DJV2> (reporting COGS of 26.8% in 2011 and 26.7% in 2010); PFIZER, 2012 FINANCIAL REPORT 15 (2012), <http://www.pfizer.com/files/annualreport/2012/financial/financial2012.pdf>, archived at <http://perma.cc/MQ8J-3GAL> (reporting COGS of 21.6% in 2011 and 22.7% in 2010).

ing 52%.⁵⁰ Generics' COGS are a higher fraction of total sales for several reasons, including lower consumer prices⁵¹ and lower R&D, compliance, and marketing costs.⁵² Although it is not a priori obvious that absolute (as opposed to fractional) manufacturing costs should be lower for generic companies,⁵³ and although hard numbers are difficult to obtain, industry experts nevertheless suggest that generics also have lower per-unit costs.⁵⁴

Biologics also face high manufacturing costs.⁵⁵ The manufacture of biologics has been characterized as "highly complex and requir[ing] high capital investments."⁵⁶ Both fixed and variable manufacturing costs are higher for biolog-

⁵⁰ Basu et al., *supra* note 39, at 33 fig.1; *see also* TEVA PHARM. INDUST. LTD., FORM 20-F: ANNUAL REPORT PURSUANT TO SECTION 12 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934, at 6 (2011), available at <http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9MTI2OTcyfENoaWxkSUQ9LTF8VHlwZT0z&t=1>, archived at <http://perma.cc/YD8P-Z7NT> (reporting COGS as 48% of sales in 2011 and similar levels in the previous four years.).

⁵¹ Lower consumer 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.

⁵² Basu et al., *supra* note 39, at 33–34.

⁵³ For example, brand-name manufacturers could potentially optimize the manufacturing process over years of experience with the drug. *See* Christopher S. Ponder, Comment, *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. *See* Prabir Basu, *Today's Hidden Crisis in Health Care: The State of Pharmaceutical Manufacturing*, RPM REP., Sept. 2008, at 2, available at http://www.nipte.org/docs/RPM_REPORT.pdf, archived at <http://perma.cc/XR2-WFSD> ("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."); *see also infra* notes 60–91 and accompanying text (discussing the lack of innovation in pharmaceutical manufacturing).

⁵⁴ *See* Mark Herlant, *Restoring the Balance: A Strategic Role for Operations*, in THE PATHWAY TO OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY 64, 68 (Thomas Friedli et al. eds., 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.").

⁵⁵ Biologics include therapeutic proteins and other products of living sources. Paradise, *supra* note 9, at 502; *see also* 42 U.S.C. § 262(i)(1) (2006) (defining "biological product" as, "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein . . . , or analogous product, or arsphenamine or derivative of arsphenamine . . . , applicable to the prevention, treatment, or cure of a disease or condition of human beings").

⁵⁶ OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY 153 (Thomas Friedli et al. eds., 2006) [*hereinafter* OPERATIONAL EXCELLENCE]. Biologics can be modified in various and sometimes unpredictable ways during their synthesis; for example, biologics can vary across production systems or batches, and even in a single production batch. Paradise, *supra* note 9, at 502–03 (noting that production and storage processes cause biologics to have high variations rates than other types of drugs); *see* Michael Butler, *Animal Cell Cultures: Recent Achievements and Perspectives in the Production of Biopharmaceuticals*, 68 APPLIED MICROBIOLOGY & BIOTECHNOLOGY 283, 286–88 (2005) (discussing variations in glycans tests).

ics than for small-molecule drugs.⁵⁷ Fractional manufacturing costs are lower, at 14% of total sales,⁵⁸ 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.⁵⁹ Even though manufacturing comprises a smaller portion of expenses for biologics, it remains a significant factor in the dynamics of market entry and market maintenance.

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

B. Lack of Innovation of Manufacturing Processes

Pharmaceutical manufacturing has lagged far behind other industries in adopting modern manufacturing techniques.⁶⁰ 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 1980s and spread through automotive, consumer goods, and other industries,⁶¹ but generally not the drug industry.⁶² This lag has resulted in overall poor operational performance in drug manufacturing,⁶³ characterized by specific related deficiencies—including excessive process rigidity, old plants and equipment, slow development and adoption of

⁵⁷ Compare Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1294 (2006) (reporting that in 2006, an average plant for biologic production was estimated to cost \$250–450 million to construct), with *Pharma Closed How Many US Plants This Year?*, EXPERTBRIEFINGS.COM (Dec. 14, 2011, 1:07 PM), <http://www.expertbriefings.com/news/pharma-closed-how-many-us-plants-this-year/>, archived at <http://perma.cc/FR8Z-5L5F> (reporting that an average plant for small-molecule drug production can be built for \$41 million). The materials for biologics manufacturing also cost many times that of small molecules. Grabowski et al., *supra*, at 1294.

⁵⁸ Basu et al., *supra* note 39, at 33 fig.1.

⁵⁹ See *id.* at 34 figs.3 & 4. One 1994–2006 study found that R&D typically comprised 26% of total sales for biologics companies versus 13% and 8% for brand-name and generic small molecule drug companies, respectively. *Id.* at 34 fig.3. The same study found that operating income for biologics companies comprised 22% of the companies' total sales, versus 19% and 12% for brand-name and generics, respectively. *Id.* at 34 fig.4.

⁶⁰ OPERATIONAL EXCELLENCE, *supra* note 56, at 24.

⁶¹ *Id.* at 30–33.

⁶² *Id.* at 24–25; see also Lawrence Yu, *Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control*, 25 PHARMACEUTICAL RES. 781, 786 (2008) (noting that in 2008, pharmaceutical development scientists had “just begun” using process simulation to support manufacturing optimization and product development, even though process simulation had been “successfully used in the chemical and oil industries since the early 1960s”).

⁶³ See Herlant, *supra* note 54, 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).

novel technology, underutilized equipment and inefficient procedures, a lack of continuous process monitoring, and significant waste.⁶⁴

Process rigidity, where manufacturing parameters remain static over the lifetime of the drug,⁶⁵ is a defining characteristic of pharmaceutical manufacturing, as opposed to other industries, where flexibility and continuous improvement are crucial for efficient and innovative manufacturing.⁶⁶ FDA oversight contributes to this process rigidity.⁶⁷ Because clinical trials are the foundation of the FDA's initial determination that an approved drug is safe and effective, formulations and manufacturing techniques used in mass production must match the processes used in the clinical trials.⁶⁸ But regulatory submissions on drug characteristics are typically based on relatively limited and shallow information.⁶⁹ Thus, the manufacturing conditions described in the initial submission become somewhat arbitrary regulatory commitments that must be kept in future manufacturing.⁷⁰

Process rigidity also encourages drug manufacturers to continue using outdated production lines and older equipment. The industry's factories have been generally described as "in terrible shape."⁷¹ Many facilities and primary production lines are quite old. Some have been operating continually since the 1960s, frequently running twenty-four hours a day, seven days a week, with only limited upgrades.⁷² Outdated and overworked facilities increase the risk of contamination of sterile products, require "repeated or extensive manual interventions," (further increasing the risk of contamination), and can even shed glass or metal shavings into the product.⁷³ One FDA Warning Letter to Ben Venue Labs, issued after a 2011 plant inspection, described a plant with "severely dented" doors

⁶⁴ See Prabir Basu, *The Current State of Pharmaceutical Manufacturing—In Search of Science*, in THE PATHWAY TO OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY, *supra* note 54, at 77, 79.

⁶⁵ OPERATIONAL EXCELLENCE, *supra* note 56, at 32.

⁶⁶ *Id.* at 48; see also THE PATHWAY TO OPERATIONAL EXCELLENCE IN THE PHARMACEUTICAL INDUSTRY, *supra* note 54, at 29 (noting that the pharmaceutical industry lags on continuous improvement).

⁶⁷ See *infra* notes 130–204 and accompanying text (discussing the hurdles to manufacturing innovation that FDA regulations create).

⁶⁸ OPERATIONAL EXCELLENCE, *supra* note 56, at 32.

⁶⁹ *Id.* at 25.

⁷⁰ *Id.*

⁷¹ Katie Thomas, *Lapses at Big Drug Factories Add to Shortages and Danger*, N.Y. TIMES, Oct. 18, 2012, at A1 (quoting Erin Fox, manager of the Drug Information Service at the University of Utah).

⁷² J. Woodcock & M. Wosinska, *Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages*, 93 CLINICAL PHARMACOLOGY THERAPEUTICS 170, 173 (2013).

⁷³ *Id.*

shedding rust into drug containers, rusty tools used for sterile line setup, and a roof leaking water into sterile areas.⁷⁴

Outdated facilities and process rigidity also reflect a broader trend of slow development and adoption of novel technologies in drug manufacturing. The industry spends little on developing new manufacturing technologies and is slow to adopt new processes once developed.⁷⁵ For example, the sorts of academic-industry collaborations that have become common both in drug discovery and in other industries' manufacturing sectors are just starting to emerge for pharmaceutical manufacturing.⁷⁶ One clear sign of the technological lag in drug manufacturing is that the industry still produces drugs step-by-step, in large batches, as opposed to using continuous manufacturing (i.e., start-to-finish production lines) like almost every other industry.⁷⁷

In addition to process rigidity, industry manufacturing procedures are plagued with inefficiencies. Inefficiencies appear in the utilization of capital resources,⁷⁸

⁷⁴ Warning Letter from the U.S. Food & Drug Admin. to Thomas J. Murphy, President & CEO, Ben Venue Labs., Inc. 1–4, 19, 20 (May 25, 2011), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM275843.pdf>, archived at <http://perma.cc/ZH6T-KPQM>.

⁷⁵ See *infra* notes 130–154 and accompanying text (explaining that many firms do not adopt process innovations out of fear of delayed FDA approval).

⁷⁶ See Todd Wallack, *Novartis to Give MIT \$65m to Find New Way to Produce Drugs*, BOS. GLOBE, Sept. 28, 2007, at A1 (reporting the development of the Novartis-MIT Center for Continuous Manufacturing and illustrating its novelty); *About C-SOPS*, C-SOPS, <http://ercforsops.org/about-c-sops>, archived at <http://perma.cc/AW28-ASJA> (last visited Feb. 10, 2014) (describing the Rutgers' Engineering Research Center for Structured Organic Particulate Systems). See generally Daniel X. Yang & Yunsoo A. Kim, *Helping Science and Drug Development to Succeed Through Pharma-Academia Partnerships*, 86 YALE J. BIO. MED. 429 (2013) (discussing academic-industry collaborations in drug discovery); Carlton Chen, *Leveraging Opportunities Through University-Industry Collaboration*, U. CONN. (July 30, 2013), <http://news.engr.uconn.edu/manufacturers-roundtable-leveraging-mfg-opportunities-through-university-industry-collaboration.php>, archived at <http://perma.cc/ME55-AYU3> (discussing the University of Connecticut's recent Manufacturers Roundtable meeting that was held to encourage further collaborations with the University of Connecticut in various manufacturing sectors).

⁷⁷ See Wallack, *supra* note 76; *About C-SOPS*, *supra* note 76. Both the Novartis-MIT Center for Continuous Manufacturing and Rutgers' Engineering Research Center for Structured Organic Particulate Systems focus on developing continuous manufacturing methods. See *Novartis-MIT Center for Continuous Manufacturing*, MASS. INST. TECHN., <http://blogs.wsj.com/health/2012/07/26/excedrin-production-resumes>, archived at <http://perma.cc/FUB3-M85J> (last visited Feb. 10, 2014); *Technology Platforms*, C-SOPS, <http://ercforsops.org/about-c-sops/technology-platforms>, archived at <http://perma.cc/33UY-49JM> (last visited Feb. 10, 2014).

⁷⁸ Relative to other industries, equipment is underutilized in the pharmaceutical manufacturing industry. In a survey of European drug plants, nearly two-thirds of plant equipment was idle at any given time. OPERATIONAL EXCELLENCE, *supra* note 56, at 60; see Herlant, *supra* note 54, at 67. Overall equipment effectiveness (the percentage of scheduled runtime a piece of equipment produces good products) averages 20–30% in the drug manufacturing industry, 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 (Jan. 1, 2009, 5:00 AM), available at <http://www.elsevierbi.com/publications/the-gold-sheet/43/001/attention-turns-to-the-business-case-for-quality-by-design>.

management of finished product inventories⁷⁹ and raw material stocks,⁸⁰ and labor practices.⁸¹

Quality tests in the drug industry are also outdated and inefficient. Pharmaceutical manufacturers ensure quality by discretely testing batches of drugs, typically at the end of production stages.⁸² These discrete tests identify out-of-specification products that must be discarded.⁸³ But discrete testing is less efficient than continuously monitoring product characteristics to guarantee quality throughout production.⁸⁴ As a result, pharmaceutical manufacturers have much higher error rates than permitted by regulation in final products. The combination of a lack of ongoing quality management and very strict final product standards leads to very high levels of unacceptable final products relative to other industries. Typically, between seven and 16% of products must be discarded in the drug industry.⁸⁵ Other industries with well-developed manufacturing, even those with less strict final product standards, usually have manufacturing processes that are more robust throughout production and thus require less end-testing and fewer product discards.⁸⁶ The unpredictability inherent in stringent end-oriented testing has both economic and human costs. A faulty product that makes it to the end of the production line before testing can contribute to drug shortages if the

⁷⁹ Pharmaceutical stock turns over on average 1–2 times per year, whereas consumer goods typically turn over 16–20 times per year and high tech goods can turn over as high as 50 times per year. OPERATIONAL EXCELLENCE, *supra* note 56, at 24–25. Slow turnover creates high inventory costs, likely justified by a desire to avoid losing any possible sales. *Id.* at 63.

⁸⁰ Xiaojun Wang, Inventory Management in a Pharmaceutical Company: Minimizing Discard Practices 25–28 (Sept. 2010) (unpublished Master of Engineering in Manufacturing dissertation, Massachusetts Institute of Technology) (on file with Massachusetts Institute of Technology Library). 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 id.* at 54–59; *see also id.* (finding in one case study that ingredient stocks at an active pharmaceutical ingredient plant could be reduced by 43% while still meeting the company's own stringent requirements for backup supplies).

⁸¹ Labor value-add time (how much time is spent adding value to the product) is typically around 20% in a pharmaceutical plant, whereas in the automotive industry, value-add time is typically around 60–70% or higher. Cox, *supra* note 78. 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* OPERATIONAL EXCELLENCE, *supra* note 56, at 57.

⁸² *See* OPERATIONAL EXCELLENCE, *supra* note 56, at 75.

⁸³ *See id.*

⁸⁴ *Id.* Continuous monitoring is more efficient because it allows manufacturers to spot errors and make corrections quicker. Anne Trafton, *Continuous Drug Manufacturing Offers Speed, Lowers Costs*, MASS. INST. TECH. (Mar. 12, 2012), <http://web.mit.edu/newsoffice/2012/manufacturing-pharmaceuticals-0312.html>, archived at <http://perma.cc/8T7T-7AL8>. Note that continuous monitoring is different from continuous manufacturing. Continuous monitoring involves constantly measuring product quality during manufacturing processes. Continuous manufacturing describes the difference between a constant-in/constant-out assembly-line system and one where large batches of a product go through separate and sequential process steps. *See* Wallack, *supra* note 76.

⁸⁵ OPERATIONAL EXCELLENCE, *supra* note 56, at 76.

⁸⁶ *Id.*

batch is discarded, or product recalls if testing fails to catch the problem before distribution.⁸⁷

Quality testing also takes a long time and disrupts manufacturing.⁸⁸ This disruption is magnified by FDA regulations requiring that any out-of-specification test results be addressed by a full investigation before retesting to validate the result or continuing the manufacturing process.⁸⁹ Quality control thus 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.⁹⁰

This dire picture is not universal in the drug industry. Some industry leaders have embraced some modern manufacturing techniques. Those leaders that have pursued manufacturing innovation have experienced concomitant gains in efficiency and continuous control over drug quality.⁹¹ But even those leaders face substantial barriers to innovative change. And overall, drug manufacturing continues to be highly inefficient and non-innovative compared both with other industries and with earlier stages in the life of a drug. These inefficiencies and outdated techniques have major implications for the industry, the healthcare system, and society as a whole.

C. Potential Benefits from Improving Manufacturing Processes

Manufacturing innovation would 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 still important implications for the industry and society.

1. Reduced Costs

Tens of billions of dollars are spent annually on manufacturing inefficiencies. Efficiency increases consequently carry large potential benefits. One study found potential yearly savings of \$19 million in COGS for a single billion-dollar

⁸⁷ See Yu, *supra* note 62, at 782; *infra* notes 108–121 and accompanying text (discussing recent contamination events and drug shortages).

⁸⁸ OPERATIONAL EXCELLENCE, *supra* note 56, at 72.

⁸⁹ 21 C.F.R. § 211.192 (2013) (“Any unexplained discrepancy . . . or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed . . .”).

⁹⁰ OPERATIONAL EXCELLENCE, *supra* note 56, at 125–26. Similarly, the process for manufacturing the main active ingredient in Schering-Plough/Merck’s cholesterol drug Vytorin reportedly includes 21.7 days of manufacturing and 63 days of testing and quality control/quality assurance. Wang, *supra* note 80, at 14.

⁹¹ See OPERATIONAL EXCELLENCE, *supra* note 56, at 82–130.

blockbuster drug, with lifetime revenue increases of \$577 million.⁹² Estimated potential savings to the pharmaceutical industry worldwide range from \$15 to \$90 billion yearly.⁹³

Another study analyzed the potential social gains from industry-wide drug manufacturing improvements.⁹⁴ The study described two possible boundary scenarios resulting from various hypothetical increases in manufacturing efficiency, which in turn would decrease the marginal cost of producing drugs.⁹⁵ In the first scenario, lower manufacturing costs result in lower prices to consumers.⁹⁶ This should occur in fully competitive markets where marginal price equals marginal cost at equilibrium.⁹⁷ But even in monopolies or oligopolies, where 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.⁹⁸ In this orthodox model, an industry-wide 20% reduction in pharmaceutical manufacturing costs, totaling between \$20 and \$30 billion,⁹⁹ would lead to estimated yearly consumer surplus gains of \$47.4 billion in the United States.¹⁰⁰

In the study's second boundary case, manufacturers stray from the orthodox market model by holding prices steady.¹⁰¹ The resulting increased cash flow from sales would tend, both theoretically and empirically, to increase firm R&D expenditures.¹⁰² An industry-wide 20% decrease in manufacturing costs, if pric-

⁹² Suresh & Basu, *supra* note 11, at 186. Revenue increases include the effect of earlier peak drug availability, measured over the lifetime of the drug. *See id.* at 185–86.

⁹³ *Id.* One early-moving major drug company, GlaxoSmithKline, has estimated that its own ongoing program of optimizing manufacturing operations will deliver annual pretax savings of approximately £2.8 billion (\$4.5 billion) by 2014. GLAXOSMITHKLINE, *supra* note 49, at 55. The program cost approximately £4.9 billion (\$7.7 billion) to implement. *Id.*

⁹⁴ Vernon et al., *supra* note 13, at 229–30, 237.

⁹⁵ *Id.* Considering these to be “boundary scenarios,” the author of the study hypothesized that “the actual effect of improved manufacturing efficiency [would] (possibly) exist[] somewhere between the two model projections. *Id.* at 230.

⁹⁶ *Id.* at 230–34.

⁹⁷ *Id.*

⁹⁸ *Id.*

⁹⁹ Suresh & Basu, *supra* note 11, at 186.

¹⁰⁰ Vernon et al., *supra* note 13, at 234 tbl.1. This study also calculates the total benefit of these savings in all future years, assuming other factors hold constant, and finds a total value of \$676.7 billion. *Id.*

¹⁰¹ *Id.* at 234–37.

¹⁰² John A. Vernon, *Examining the Link Between Price Regulation and Pharmaceutical R&D Investment*, 14 HEALTH ECON. 1, 3, 6 (2005) (noting that reducing price regulation encourages firms to invest more in R&D); *see* F. M. Scherer, *The Link Between Gross Profitability and Pharmaceutical R&D Spending*, 20 HEALTH AFF. 216, 220 (2001) (explaining that firms are rent-seeking with R&D and are thus more likely to invest in R&D as profit opportunities increase). The intuition behind this result is that firms invest in R&D by funding projects in order from most promising to least promising until the marginal expected return for a project equals the marginal cost of additional capital. *See* Vernon et al., *supra* note 13, at 235–37. When a firm's cash flow increases, as here through lower manufacturing costs and steady prices, the available cash has a lower cost of capital than borrowing

es hold constant, would lead to a \$3.9 billion one-time increase in annual R&D flows.¹⁰³ The present value of that increase, taking into account patterns of R&D growth over time, is \$110.4 billion.¹⁰⁴ Increases in pharmaceutical R&D, in turn, have large effects on social welfare because newly discovered drugs can improve health outcomes and improve life expectancy. One scholar estimated that each \$1345 invested in pharmaceutical R&D leads to health increases with a value of one U.S. life-year.¹⁰⁵ Using this estimate, a 20% reduction in manufacturing costs would result in an annual gain of 5.7 million life-years through increases in R&D spending.¹⁰⁶ Using a benchmark approximate value of \$100,000 for a life-year, the annual value of this health increase would be \$574 billion.¹⁰⁷

Even though the study's two estimates are stylized, the social gains of even moderately increased pharmaceutical manufacturing efficiency are easily measured in the tens or hundreds of billions of dollars.

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.¹⁰⁸ Resulting improvements in drug quality could improve human health and well-being by reducing quality failures such as contamination events and drug shortages.

Contamination events and other major quality control failures cause loss of life and decrease confidence in the industry, both of which may lead to even further health ramifications.¹⁰⁹ Such quality failures include the Chinese heparin

funds or issuing new equity. *Id.* Accordingly, more R&D projects are worth funding. Vernon et al., *supra* note 13, at 235–37. This logic relies on the theoretical assumption that capital markets are imperfect.

¹⁰³ Vernon et al., *supra* note 13, at 236 tbl.2.

¹⁰⁴ *Id.*

¹⁰⁵ Frank R. Lichtenberg, *Sources of U.S. Longevity Increase, 1960–1997*, at 17, (Nat'l Bureau of Econ. Research, Working Paper No. 8755, 2002), available at http://www.nber.org/papers/w8755.pdf?new_window=1, archived at <http://perma.cc/9TMZ-EX8G>.

¹⁰⁶ See Vernon et al., *supra* note 13, at 236 tbl.3. Vernon calculated an all-years present value gain of 82.1 million life years; using his estimated 7% discount rate, this gives a yearly gain of 5.7 million life-years. *Id.*

¹⁰⁷ See *id.* The study calculated an \$8.2 trillion present value of the all-years increase, which equates to a yearly gain of approximately \$574 billion using a 7% discount rate. *Id.*

¹⁰⁸ See Basu, *supra* note 64, at 78.

¹⁰⁹ See Maame Ewusi-Mensah Frimpong, U.S. Deputy Assistant Attorney Gen., Address at the 2013 CBI Pharmaceutical Compliance Congress (Jan. 29, 2013) (transcript available at <http://www.justice.gov/iso/opa/civil/speeches/2013/civ-speech-130129.html>, archived at <http://perma.cc/RV9E-6YPP>) (“Weak enforcement that encourages deviations from [good manufacturing practices] and noncompliance in this area affects the entire industry, as it erodes the confidence of the American public in our drug system.”); see also Larry Rosania, *Heparin Crisis 2008: A Tipping Point for In-*

crisis of 2008 that killed over 81 people¹¹⁰ and the 2012 meningitis outbreak from contaminated steroids, which has so far killed 64 people and sickened 751 more across 20 states.¹¹¹ Using outdated and decrepit manufacturing equipment directly contributes to the likelihood of contamination events and quality problems.¹¹²

Failing to innovate also contributes. Greater process understanding, increased in-line monitoring, and more modern techniques all could 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.¹¹³ Most companies, however, have not embraced this type of innovation, in part for the reasons described below.

Improving manufacturing could also help alleviate drug shortages. Drug shortages are an ongoing and increasing problem.¹¹⁴ Shortages are estimated to

created FDA Enforcement in the Pharma Sector?, 65 FOOD & DRUG L.J. 489, 491–92 (2010) (describing loss of life resulting from quality control failures).

¹¹⁰ Gardiner Harris, *F.D.A. Identifies Tainted Heparin in 11 Countries*, N.Y. TIMES (late ed.), Apr. 22, 2008, at 1 (reporting 81 deaths in the crisis); see also Rosania, *supra* note 109, at 491–91 (attributing 150 deaths to the crisis).

¹¹¹ *Multistate Outbreak of Fungal Meningitis and Other Infections—Case Count*, CDC, <http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html>, archived at <http://perma.cc/9GER-VSL2> (last updated Oct. 23, 2013); see Andrew Pollack & Sabrina Tavernise, *Oversight Failures Documented in Meningitis Outbreak*, N.Y. TIMES, Nov. 22, 2012, at A27. The affected steroids were manufactured in a compounding pharmacy not directly subjected to FDA regulation. *Id.* The industry-wide innovation deficiency created by regulation and intellectual property failures, however, directly impacts the technologies and techniques available to compounding pharmacies as well as more typical drug manufacturers.

¹¹² See Margaret Hamburg, Speech to the Annual Meeting of the Generic Pharmaceutical Manufacturers Association (Feb. 22, 2013) (transcript available at <http://www.fda.gov/NewsEvents/Speeches/ucm340870.htm>, archived at <http://perma.cc/C3UK-UESA>) (observing that there have been “too many quality lapses throughout the pharmaceutical industry over the past few years[,]” connecting quality problems to “aging facilities,” and noting that “instilling quality is equally important for . . . future pipeline[s] as well”).

¹¹³ See Eunah Lee et al., *High-Throughput Analysis of Pharmaceutical Tablet Content Uniformity by Near-Infrared Chemical Imaging*, 21 SPECTROSCOPY 24, 24–25 (2006), available at <http://www.spectroscopyonline.com/spectroscopy/data/articlestandard/spectroscopy/472006/387571/article.pdf>, archived at <http://perma.cc/3YF-84K8> (discussing near-infrared chemical imaging, which measures active ingredients in drug tablets without destroying the samples).

¹¹⁴ See Kevin Born, *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) (noting that in 2011, there were 267 such drug shortages, up from 211 in 2010, 166 in 2009, and 61 in 2005); see also *id.* (noting that this trend is expected to continue, with even more shortages expected in the future). 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 user level.” CTR. FOR DRUG EVALUATION & RESEARCH, MAPP 6003.1, MANUAL OF POLICIES & PROCEDURES 7 (2012).

have monetary costs totaling \$416 million per year¹¹⁵ and unknown human costs in terms of patients dying, suffering adverse reactions, or delaying treatment.¹¹⁶ In 2011, 73% of shortages were sterile injectable drugs,¹¹⁷ many of which are important front-line cancer treatments in widespread use, but shortages exist across all dosage forms.¹¹⁸ The ultimate causes of drug shortages are debated, but most are closely linked to manufacturing problems.¹¹⁹ In 2011, 46% of drug 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.”¹²⁰ Manufacturing delay or capacity issues caused another 19% of shortages, such as “when embedded quality problems with one product force 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).”¹²¹ As a result, manufacturing innovation and improvement to increase robustness, flexibility, and drug quality could significantly help shortages.

The human costs of manufacturing failures are large and apparently increasing. Improving innovation in manufacturing could help to reduce the incidence of manufacturing quality failures, especially those failures resulting in harmful contamination events and direct human injury. Manufacturing innovation and the resulting increase in quality and flexibility could also reduce the incidence of drug shortages. Presumably, more reliable and better controlled manufacturing could increase drug uniformity and quality, which could then im-

¹¹⁵ See COLEEN CHERICI ET AL., NAVIGATING DRUG SHORTAGES IN AMERICAN HEALTHCARE: A PREMIER HEALTHCARE ALLIANCE ANALYSIS 6 (2011), <https://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf>, archived at <http://perma.cc/LJB2-LAD6> (indicating that shortages result in increased payments for drugs and shipping of approximately \$200 million annually); Rola Kaakeh et al., *Impact of Drug Shortages on U.S. Health Systems*, 68 AM. J. HEALTH-SYSTEM PHARMACY 1811, 1814 (2011) (reporting that increased labor costs of time spent by pharmacists, doctors, and nurses dealing with drug shortages cost an estimated additional \$216 million annually).

¹¹⁶ See Born, *supra* note 114, at 239 (discussing the many potential adverse consequences patients may face when doctors are forced to alter their medications due to drug shortages); *Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety*, ISMP MEDICATION SAFETY ALERT!: ACUTE CARE EDITION, (Inst. for Safe Medication Practices, Horsham, Pa.), Sept. 23, 2010, at 1, 1, available at <http://www.ismp.org/newsletters/acutecare/articles/20100923.asp>, archived at <http://perma.cc/WK3-2YH4> (same).

¹¹⁷ S.L. Kweder & S. Dill, *Drug Shortages: The Cycle of Quantity and Quality*, 93 CLINICAL PHARMACOLOGY THERAPEUTICS 245, 246 fig.1 (2013); Woodcock & Wosinska, *supra* note 72, at 170.

¹¹⁸ Bruce A. Chabner, *Drug Shortages—A Critical Challenge for the Generic-Drug Market*, 365 NEW ENG. J. MED. 2147, 2147–48 (2011).

¹¹⁹ Woodcock & Wosinska, *supra* note 72, at 170–71; see CHERICI ET AL., *supra* note 115, at 2–3; Chabner, *supra* note 118, at 2147–48.

¹²⁰ Kweder & Dill, *supra* note 117, at 247.

¹²¹ *Id.* Twelve percent of shortages were due to discontinuations, which may also result from quality problems. *Id.* at 247 fig.2; see Patricia M. Danzon & Nuno Sousa Pereira, *Vaccine Supply: Effects of Regulation and Competition*, 18 INT’L J. ECON. BUS. 239, 265 (2011) (noting that because vaccine manufacturers are “[f]aced with low prices and volatile demand, [they] have chosen to exit rather than incur the significant costs of bringing manufacturing capacity up to the high standards required”).

prove the predictability of medical treatment. Overall, manufacturing innovation has the potential for major human health and industry cost benefits.

II. THE FAILURE OF INNOVATION POLICY IN PHARMACEUTICAL MANUFACTURING

Innovation in drug manufacturing is vital for a well-functioning health system, and the innovation landscape is deeply shaped by legal rules and regulatory structures. The limited literature that previously has addressed innovation problems in pharmaceutical manufacturing has focused largely on firm culture and executive focus.¹²² Although these explanations undoubtedly contain some truth, they do not address the role that legal rules and innovation policy play in slowing innovation. 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

¹²² See, e.g., OPERATIONAL EXCELLENCE, *supra* note 56, at 32 (“Manufacturing has not been seen as central in producing competitive advantage.”); Bowman Cox, *Slogging Toward Quality by Design*, GOLD SHEET (Dec. 20, 2012, 12:00 PM), available at <http://www.elsevierbi.com/publications/the-gold-sheet/46/12/slogging-toward-quality-by-design> (citing a report by 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. See OPERATIONAL EXCELLENCE, *supra* note 56, at 32; Cox, *supra*. 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 OPERATIONAL EXCELLENCE, *supra* note 56, at 155 (noting that “[a]s 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, *Financial Justification for QbD and Cost of Regulation Compliance*, PROFITABILITY THROUGH SIMPLICITY (May 22, 2012, 12:33 PM), <http://pharmaceuticalscoatings.blogspot.com/2012/05/financial-justification-for-qbd-and.html>, archived at <http://perma.cc/HEZ6-GCGH> (“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, t]he current blockbuster business model absorbed all of the manufacturing deficiencies. Shareholders got accustomed to the fast paced introduction of new drugs and profits.”). Furthermore, blockbusters may have both higher potential profits and lower manufacturing costs than other drugs. Matthew Harper, *The Death of the Blockbuster Drug*, FORBES (May 28, 2010, 6:00 AM), <http://www.forbes.com/sites/sciencebiz/2010/05/28/the-death-of-the-blockbuster-drug/>, archived at <http://perma.cc/HZ5X-5K99>. High volume means fixed costs are lower per unit. *Special Report: Blockbuster Death and Growth of Generics*, PHARMKON (Feb. 11, 2013), <http://pharmakon.me/2013/02/11/special-report-blockbuster-death-and-growth-of-generics/>, archived at <http://perma.cc/J42G-7DMA>. Marginal costs may also decrease due to economies of scale, especially for simply formulated small-molecule drugs. See *id.* Thus, if blockbusters are management-paradigm-defining, effort will tend to be focused away from manufacturing innovation. Although 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 Article.

known, making manufacturing innovations appropriate targets for intellectual property incentives.¹²³ The intellectual property exclusivity incentives available for manufacturing innovation, however, are less effective and have more serious negative effects on innovation than those available for drug discovery and development.¹²⁴

Also like drug discovery and development, drug manufacturing is tightly regulated to ensure public safety.¹²⁵ Regulatory structures for drug discovery and development create incentives for innovation and interact cooperatively with intellectual property to strengthen those incentives.¹²⁶ Conversely, regulatory oversight for drug manufacturing actively inhibits innovation.¹²⁷

Section A of this Part describes how the FDA's regulations inhibit manufacturing innovation in the pharmaceutical industry.¹²⁸ Section B discusses potential innovation incentives from patents, FDA-administered market exclusivity, and trade secrets.¹²⁹

A. Regulatory Hurdles to Innovation in Pharmaceutical Manufacturing

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, the FDA is statutorily authorized to provide market exclusivity as a reward to drug companies for certain behaviors.¹³⁰ The FDA's regulatory oversight also provides an indirect incentive to discover and develop new drugs. Firms develop drugs in several stages. Typically, the firm takes the new drug through three phases of clinical trials as an Investigational New Drug ("IND") and then files an extensive and expensive New Drug Application ("NDA") to win approval to

¹²³ See *infra* notes 248–269 and accompanying text (discussing the safe harbor under the Hatch-Waxman Act for using patented processes); *infra* notes 284–331 and accompanying text (analyzing the benefits and shortcomings of trade secrets for pharmaceutical manufacturing). The same may be true for manufacturing in most industries. Other industries, however, generally do not need as large of incentives to overcome the major regulatory hurdles faced by drug manufacturers. See *infra* notes 130–204 and accompanying text.

¹²⁴ See *infra* notes 205–331 and accompanying text (discussing intellectual property in the pharmaceutical industry).

¹²⁵ See *infra* notes 130–204 and accompanying text (discussing FDA regulations on pharmaceutical manufacturing).

¹²⁶ See *infra* notes 130–136 and accompanying text (explaining that FDA regulations induce drug discovery by creating barriers to entry that prevent competitors from entering the market); *infra* notes 205–212 and accompanying text (discussing the roles of patents and FDA regulatory exclusivity in promoting drug discovery).

¹²⁷ See *infra* notes 130–204 and accompanying text (explaining the hurdles to innovation that FDA regulations create for pharmaceutical manufacturing).

¹²⁸ See *infra* notes 130–204 and accompanying text.

¹²⁹ See *infra* notes 205–331 and accompanying text.

¹³⁰ See *infra* notes 270–283 and accompanying text (describing FDA market exclusivity).

sell the drug.¹³¹ This costly regulatory gantlet creates a barrier to entry that can keep competitor drugs off the market.¹³² By excluding competitors, this regulatory system effectively extends monopoly pricing for the innovator company and increases the reward for the initial innovation.¹³³ This effect operates on both pioneer¹³⁴ and generic companies.¹³⁵ Finally, as discussed below, the FDA ap-

¹³¹ An IND is a filing that must be made with the FDA to allow a new drug to be transported across states before the drug has received marketing approval and before commencing clinical trials (Phase I–III testing). *Investigational New Drug (IND) Application*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm>, archived at <http://perma.cc/E8R6-HFZZ> (last visited Feb. 25, 2014). The drug is classified as an IND during Phase I–III trials. See *New Drug Application*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm>, archived at <http://perma.cc/R8MT-H7LF> (last visited Feb. 25, 2014). Phase I is the initial stage of clinical trials for an IND and focuses on safety. *The FDA's Drug Review Process: Enduring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>, archived at <http://perma.cc/U2KT-9Y8U> (last visited Feb. 15, 2014). Phase II trials focus on ensuring the drug is effective. *Id.* Finally, Phase III testing focuses on safety and effectiveness across varying populations. *Id.* If the drug passes Phase I–III trials, the manufacturer then files an NDA. See *New Drug Application*, *supra*. If the FDA approves the NDA, then the new drug is ready for market. See *id.* For a broader overview of the drug development and approval process, see generally MARK P MATHIEU, *NEW DRUG DEVELOPMENT: A REGULATORY OVERVIEW* (2008). Biologics require a Biologic License Application (“BLA”) instead of an NDA. *Biologics License Applications (BLA) Process (CBER)*, U.S. DEP’T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/>, archived at <http://perma.cc/BEF4-BM2K> (last updated Feb. 13, 2010).

¹³² See Rebecca S. Eisenberg, *The Shifting Functional Balance of Patents and Drug Regulation*, 20 HEALTH AFF. 119, 121 (2001).

¹³³ See *id.*

¹³⁴ 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. Panos 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, 459 (2007). Four other branded statins with similar methods of action have also been widely marketed: Zocor, Leschol, Baychol, and Pravachol. *Id.* at 457. 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 457, 459–61, 464. Thus, because later market entrants face lower revenues, but the same high regulatory approval costs, marginal market entrants (a hypothetical sixth branded statin) are deterred from entering. 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 competition, and thus preserve monopoly or oligopoly pricing power.

¹³⁵ Although the costs of generic approval are much lower, so are potential profits, which keeps the regulatory barrier to entry significant. Eisenberg, *supra* note 132, at 121. In some circumstances, however, the first generic entrant can obtain a 180-day window of exclusivity because the generic company usually sells its drugs at near-monopoly prices within that window and, as a result, increases profits tremendously. *Id.* at 122. No other generic companies have the benefit of this extra profit. See *id.*

proval process strengthens the exclusivity effects of drug patents by making the patents much harder to invent around.¹³⁶

In the context of drug manufacturing, however, the FDA not only fails to create incentives for innovation, it imposes significant limits on innovation.¹³⁷ First, institutional resistance to approving novel technologies restrains innovation during the NDA process. As a result, firms avoid innovative technologies in NDAs for fear of delays in receiving marketing approval. Subsection 1 discusses these preapproval regulatory barriers.¹³⁸ Second, some aspects of manufacturing are mandated by current Good Manufacturing Practices (“cGMP”) regulations, which create de facto technological standards that are not subject to firm-level innovation. Subsection 2 discusses these de facto standards and their effect on innovation.¹³⁹ Third, postapproval 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. Subsection 3 analyzes these postapproval barriers.¹⁴⁰ All of these regulatory constraints are generally imposed without considering their impact on manufacturing innovation and efficiency.¹⁴¹

1. Preapproval 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 methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug,”¹⁴² which must be approved by the FDA.¹⁴³ The agency has historically been reluctant to accept unfamiliar technologies, especially in NDAs.¹⁴⁴

¹³⁶ See *infra* notes 223–269 and accompanying text (discussing patents’ role in the pharmaceutical industry).

¹³⁷ This Article does 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 that 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).

¹³⁸ See *infra* notes 142–154 and accompanying text.

¹³⁹ See *infra* notes 155–167 and accompanying text.

¹⁴⁰ See *infra* notes 168–204 and accompanying text.

¹⁴¹ OPERATIONAL EXCELLENCE, *supra* note 56, at 126 (“[In] 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.”).

¹⁴² 21 U.S.C. § 355(b)(1)(D) (2012); see 21 C.F.R. § 314.50(d)(1) (2013) (specifying the manufacturing and chemical disclosures that must be made on an FDA application). For ANDAs, see 21 U.S.C. § 355(j)(2)(A), which outlines the specific information that must be contained in a ANDA

For example, for roughly a decade beginning in the 1960s, several companies filed NDAs that included manufacturing controls that used a technique known as high performance liquid chromatography (“HPLC”).¹⁴⁵ At the time, HPLC was considered technically superior to the previously dominant technology of thin-layer chromatography.¹⁴⁶ The FDA, however, was familiar with the older technology and had approved its use. Thin-layer chromatography was also used in the United States Pharmacopoeia (“USP”), a source of drug standards.¹⁴⁷ Conversely, FDA reviewers were relatively unfamiliar with HPLC. As a result, getting approval for an NDA that used HPLC was nearly impossible for that decade; firms had to replace HPLC with an alternate technique to receive approval.¹⁴⁸ Eventually, the FDA was persuaded to accept HPLC as a validated technique, and it is now widely used.¹⁴⁹

HPLC provides an early example of the difficulty pharmaceutical firms face in trying to get new technology approved after the FDA started tightly regulating pharmaceutical manufacturing processes. HPLC also provides an unusual example of firms persistently trying to obtain FDA approval of a new technique, despite initial FDA rejections. Firms have learned from the HPLC experience—and other similar situations—that even if a sponsor can eventually get FDA acceptance of an innovation, there is a risk of major delay in getting approval. This lag in approval has very high costs for sponsor companies because any delay cuts into the patent-protected period of market exclusivity, and brand companies make the vast majority of their profits during this period.¹⁵⁰

Consequently, companies have very strong incentives to avoid incorporating any new technologies in NDAs. A Pfizer executive testified about this effect to the FDA, describing an initial NDA draft that included two parallel ways to measure a drug’s characteristic: the older method required shipping a sample 3500 miles, from Ireland to New Jersey, and took a week to get results, whereas the newer method could be done on-site in the manufacturing plant in a matter of

application, and 21 C.F.R. § 314.94(a)(9), which describes the information that must be included in an ANDA manufacturing application, including a description of the utilized equipment.

¹⁴³ 21 U.S.C. § 355(b)(1)(D), (j)(2)(A).

¹⁴⁴ See CARPENTER, *supra* note 137, at 67–68 (providing a persuasive account of the FDA’s risk-aversion as based in concerns of personal and individual reputation).

¹⁴⁵ Interview with Ajaz Hussain, *supra* note 1.

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ *Id.*

¹⁴⁹ See generally GEORGE LUNN, HPLC METHODS FOR RECENTLY APPROVED PHARMACEUTICALS (1st ed. 2005) (detailing HPLC methods for assays of hundreds of recently approved drugs).

¹⁵⁰ See CARPENTER, *supra* note 137, at 637. See generally 21 C.F.R. § 314.108 (2013) (providing for market exclusivity).

minutes.¹⁵¹ 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.¹⁵² Even though the FDA does not have an explicit policy of denying preapproval innovations, firms' realistic fears of delay consistently keep novel technologies out of NDAs.¹⁵³ Because other regulatory barriers make changing manufacturing procedures postapproval difficult,¹⁵⁴ this preapproval barrier has effects that 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.¹⁵⁵ Generally, the FDA avoids technology mandates; in terms of innovation, this is beneficial, as innovation theory recognizes that innovation can be stifled when regulators require the use of specific technologies.¹⁵⁶ 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,¹⁵⁷ these requirements are goal-oriented performance standards.¹⁵⁸ Nevertheless, the industry effectively creates de facto technology mandates by adhering tightly to technical examples in cGMP guidance

¹⁵¹ DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., SCIENCE BOARD MEETING 140–43 (2001), available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3799t1_02.pdf, archived at <http://perma.cc/NC45-KEDT>.

¹⁵² *Id.*

¹⁵³ *See id.*

¹⁵⁴ *See infra* notes 168–204 and accompanying text (discussing procedural and substantive barriers to postapproval innovation).

¹⁵⁵ *See generally* 21 U.S.C. § 351(a)(2)(B) (2012) (“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 . . . with current good manufacturing practice . . .”).

¹⁵⁶ *See* U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 32, at 2 (technology mandates); Gaia J. Larsen, *Skewed Incentives: How Offshore Drilling Policies Fail to Induce Innovation to Reduce Social and Environmental Costs*, 31 STAN. ENVTL. L.J. 139, 165–74 (2012) (innovation theory); Andries Nentjes et al., *Technology-Forcing Through Environmental Regulation*, 23 EUR. J. POL. ECON. 903, 903–04 (2007) (same).

¹⁵⁷ *See* 21 C.F.R. § 211.46 (2013) (ventilation of production buildings); *id.* § 211.67 (equipment maintenance and cleaning); *id.* § 211.188 (production and control records).

¹⁵⁸ *See, e.g., id.* § 211.63 (“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. *Id.* § 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.*

documents which causes even more severe consequences than the common practice of treating guidance as effectively binding.¹⁵⁹ As a result, the industry narrows the diversity of acceptable technologies.

The most pervasive example of industry reliance on cGMP examples is seen in the industry's reaction to the FDA's 1987 *Guideline on General Principles of Process Validation*.¹⁶⁰ 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."¹⁶¹ To illuminate this broad principle, the FDA included a single example: the Association for the Advancement of Medical Instrumentation's ("AAMI") *Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices*, which required three repetitions.¹⁶² From this example, and just a few others mentioning three validation batches, the industry almost uniformly accepted a procedure of using exactly three batches for validation of every process—whether or not three batches was actually “a sufficient number of times to assure reliable and meaningful results,”¹⁶³ as the guidance's principle requires. The industry's reliance on the three-batch regimen continues today, although the FDA has recently sought to roll it back,¹⁶⁴ and in 2011 replaced the 1987 guidance altogether.¹⁶⁵

¹⁵⁹ See *Drugs*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm>, archived at <http://perma.cc/PMH4-72H3> (last updated Sept. 16, 2013) (observing that the industry adopted a certain standard based solely on a simple example provided in FDA guidelines). Guidance is explicitly nonbinding and includes disclaimers to that effect. See U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 32, at 2 (“FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities.”).

¹⁶⁰ See generally U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., *GUIDELINE ON GENERAL PRINCIPLES OF PROCESS VALIDATION* (1987), available at <http://babel.hathitrust.org/cgi/pt?id=mdp.39015029699587;view=1up;seq=1>, archived at <http://perma.cc/X2Q4-H3U3>; *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Production and Process Controls*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#5>, archived at <http://perma.cc/S2ZS-F48K> (last updated Sept. 16, 2013) (discussing the industry and FDA reaction to the FDA's 1987 guidelines).

¹⁶¹ U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 160, at 16.

¹⁶² *Id.* at 16 n.7 (“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.’”).

¹⁶³ See *id.* at 16 (imposing this sufficiency requirement); *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Production and Process Controls*, *supra* note 160 (discussing the industry and FDA reaction to the FDA's 1987 guidelines).

¹⁶⁴ See *Drugs*, *supra* note 159 (noting that the drug industry adopted a three-batch standard based in part on the 1987 Guidelines and specifying that the three-batch standard should not be generally applied).

¹⁶⁵ See generally U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., *GUIDELINE FOR INDUSTRY: PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES* (2011), available

The industry thus self-imposes technological standards by adhering to guidance examples over principles. This self-limitation is based on firms' desires to avoid regulatory delay or uncertainty. The limitation also reflects the industry's preference for regulatory compliance over quality.¹⁶⁶ Like other technological standards, adhering to guidance examples hinders innovation. The FDA has recently sought to deal with this industry-imposed restriction by simply refusing to include examples in guidance documents.¹⁶⁷ Other innovation-increasing changes may shift industry behavior from this pattern as well.

3. Postapproval Manufacturing Changes: Procedural and Substantive Barriers

Innovation in manufacturing can also take place after FDA approval of a drug and its manufacturing method. The process of continual improvement is central to manufacturing efficiency in other industries. Larger, discrete innovations can also be incorporated to improve production. Intuitively, manufacturers that make a product for years should be better at the process because of their experience, gained and applied through process tweaks and improvements. This assumption, however, relies entirely on manufacturers' ability to innovate manufacturing methods after FDA approval. In the petroleum processing industry, for instance, continuous improvement of larger, discrete processing inventions has been as valuable as the discrete inventions themselves.¹⁶⁸ In contrast, the process of improvement in drug manufacturing faces substantial hurdles from the FDA, including both procedural barriers in the form of regulatory filings¹⁶⁹ and substantive barriers in the form of regulatory lock-in based on the empirical basis of persistent drug specifications.¹⁷⁰

at <http://www.fda.gov/downloads/Drugs/0%20%20%20%20/Guidances/UCM070336.pdf>, archived at <http://perma.cc/GP6Q-XBQH>.

¹⁶⁶ See 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. . . . [They] exist to implement and maintain the quality system required by regulatory health agencies and regulations.").

¹⁶⁷ See Interview with Emil Ciurczak, Consultant, Doramaxx Consulting (May 8, 2013) (noting that this approach is increasingly frequent). For example, one recent FDA manufacturing equipment draft guide reads: "When the [scale-up and postapproval changes ("SUPAC")] equipment addenda were published with tables referencing specific equipment, the tables were misinterpreted as equipment required by FDA." U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SUPAC: MANUFACTURING EQUIPMENT ADDENDUM 6 (2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346049.pdf>, archived at <http://perma.cc/WBT6-XTQL>. As a result, the FDA goes on to say, the "revised draft SUPAC addendum contains general information on SUPAC equipment and no longer includes tables referencing specific equipment." *Id.*

¹⁶⁸ John L. Enos, *A Measure of the Rate of Technological Progress in the Petroleum Refining Industry*, 6 J. INDUS. ECON. 180, 187–93 (1958).

¹⁶⁹ See *infra* notes 171–183 and accompanying text.

¹⁷⁰ See *infra* notes 184–204 and accompanying text.

a. Procedural Barriers from Regulatory Filings

The FDA's requirements that manufacturing changes be registered and approved impose the greatest procedural barrier for manufacturing innovation.¹⁷¹ After receiving marketing approval, a sponsor must notify the FDA if it makes any changes to an approved application.¹⁷² Changes are categorized as major, moderate, or minor.¹⁷³ Substantial regulatory submissions are required for major and moderate changes.¹⁷⁴ Major changes require agency preapproval before implementation.¹⁷⁵ 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.¹⁷⁶ Minor changes, on the other hand, must be detailed in an annual report.¹⁷⁷ For changes in any category, the drug sponsor must evaluate the change's effects on product safety and efficacy and illustrate those effects through appropriate studies to determine whether a supplement is needed.¹⁷⁸

The procedure for getting any change 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 the FDA. Perhaps even more important, a supplement raises risks that the FDA might not approve the submission, which decreases the expected benefit of a change, and that the FDA might reopen previously approved and settled manufacturing issues and find new problems with the old method.

Overall, the system creates a substantial regulatory burden for postapproval manufacturing innovations, with correspondingly larger burdens for larger changes.¹⁷⁹ Such procedural costs, when applied to every change, may complete-

¹⁷¹ OPERATIONAL EXCELLENCE, *supra* note 56, at 71.

¹⁷² 21 C.F.R. § 314.70(b)–(d) (2013). Major notifications come in the form of an sNDA.

¹⁷³ *Id.*

¹⁷⁴ *Id.* § 314.70(b), (c). Moderate changes include changes to the container closure system that do not affect drug quality, *id.* § 314.70(c)(2)(i); removing a test or relaxing a requirement to comply with an official drug compendium, *id.* § 314.70(c)(2)(iii); and, for biologics, changes in production scale that involve changing equipment or replacement of equipment with differently designed equipment that does not otherwise change the production process, *id.* § 314.70(c)(2)(ii)(A)–(B).

¹⁷⁵ *Id.* § 314.70(b)(3). In addition to the actual regulatory procedural hurdles, the requirement of regulatory submissions creates intrafirm hurdles, because innovative ideas must be transferred from the manufacturing department to the separate regulatory compliance department.

¹⁷⁶ *Id.* § 314.70(b)(2)(iv). 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." *Id.* § 314.70(b). They also include changes to the formulation or specification of the drug, including inactive ingredients. *Id.* § 314.70(b)(2)(i).

¹⁷⁷ *Id.* § 314.70(d).

¹⁷⁸ 21 U.S.C. § 356a(b) (2012).

¹⁷⁹ See *supra* notes 171–178 and accompanying text. Applications also burden the FDA, which has been "overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years." Yu, *supra* note 62, at 782. In 2005 and 2006, the Office of Generic Drugs alone received over 3000 such manufacturing change supplements. *Id.* Over 1600 supplements were filed for branded pharmaceuticals and over 800 for biologics. U.S. DEP'T OF HEALTH & HUMAN

ly prevent the type of continuous improvement that has been so successful in driving efficiency in other industries.¹⁸⁰ Additionally, the costs associated with small changes likely create a mindset that all changes are to be avoided as overly troublesome and unprofitable. This mindset may shift efforts away even from larger, net-beneficial innovations.¹⁸¹ This reality of procedural barriers is also in significant tension with the underlying theoretical goal that Good Manufacturing Processes be “current.”¹⁸²

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.¹⁸³ From a structural perspective, a central pillar of manufacturing innovation in other industries is continuous improvement through frequent small changes. Those small changes are the least likely to justify the expense of regulatory ap-

SERVS., U.S. FOOD & DRUG ADMIN., FY 2008: PERFORMANCE REPORT TO THE PRESIDENT AND THE CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT 22 (2008), available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM209479.pdf>, archived at <http://perma.cc/AH8C-5T8R>. Of the latter two sets, approximately one-third of supplements required prior approval and two-thirds did not. *Id.* Especially for changes which require FDA approval before implementation, this can result in process delays of months to manufacturers and major costs to the FDA. *See id.* at 23. Evaluating manufacturing supplements makes up roughly 11% of the FDA’s application workload. Prescription Drug User Fee Rates for Fiscal Year 2013, 77 Fed. Reg. 45639, 45641 tbl.4 (Aug. 1, 2012).

¹⁸⁰ *See* Yu, *supra* note 62, 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.”).

¹⁸¹ *See* OPERATIONAL EXCELLENCE, *supra* note 56, at 160 (noting that although regulatory barriers may hinder innovation, some firms may use the barriers as an excuse for not investing in and successfully improving on manufacturing processes).

¹⁸² *Facts About Current Good Manufacturing Practices (cGMPs)*, DEP’T HEALTH & HUMAN SERVICES, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm>, archived at <http://perma.cc/WAX5-PJBV> (last updated May 2, 2013). According to the FDA, the flexibility in cGMP regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. *Id.* 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. *Id.* 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.” *Id.* This theoretical requirement for continuous improvement is heavily contradicted by both agency and industry practice as described throughout this Article.

¹⁸³ *See* OPERATIONAL EXCELLENCE, *supra* note 56, at 160. Procedural expenses are not unique to the pharmaceutical industry, but are lower even in other closely-regulated industries. In the aeronautics industry, for example, producers of parts for airplanes must obtain Federal Aviation Administration (“FAA”) approval prior to manufacturing airplane parts. *See* 14 C.F.R. § 21 (2013). The FAA must be notified of, and can review, any change in manufacturing procedure that could affect the airworthiness of a part. *See, e.g., id.* §§ 21.93–97 (regarding approval of changes to type certificate); *id.* §§ 21.139, 21.150, 21.309, 21.320, 21.609, 21.620 (regarding notification and review of changes in manufacturing facilities or quality systems). Notification and review, however, do not require preapproval, thus reducing time and cost barriers.

proval, so the path of innovation may be entirely foreclosed for drug manufacturers. In addition to the procedural barriers imposed by FDA regulations, the regulations also create substantive barriers to manufacturing 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.¹⁸⁴ The FDA's empirical approval of a drug is based on clinical trials using that drug as it existed when used in the clinical trials.¹⁸⁵ For most drug characteristics, including those that do not affect treatment outcomes or safety, whatever values may exist at the time of regulatory submission become the benchmark for measuring future drugs.¹⁸⁶ 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 batches¹⁸⁷ of the drug as used for clinical testing.¹⁸⁸ Specifications for the drug are set based on the average values and variability of those initial

¹⁸⁴ See OPERATIONAL EXCELLENCE, *supra* note 56, at 25; Allison Stoddart, Note, *Missing After Mensing: A Remedy for Generic Drug Consumers*, 53 B.C. L. REV. 1967, 1968 (2012).

¹⁸⁵ See OPERATIONAL EXCELLENCE, *supra* note 56, at 25.

¹⁸⁶ See *id.* As one commentator has explained:

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."

Id.

¹⁸⁷ See *supra* notes 160–167 and accompanying text (explaining that manufacturers blindly and detrimentally use three batches to follow an example provided in the 1987 FDA *Guideline on General Principles of Process Validation*).

¹⁸⁸ See U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DISSOLUTION TESTING OF IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS 3, 5 (1997) [hereinafter DISSOLUTION], available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070237.pdf>, archived at <http://perma.cc/A2AD-NCYW>; see also U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: Q3A IMPURITIES IN NEW DRUG SUBSTANCES (2008) [hereinafter Q3A IMPURITIES], available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127984.pdf>, archived at <http://perma.cc/46SU-CTA4> ("The selection of impurities in a new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process.").

batches, and all future batches of the drug are required to meet those specifications.¹⁸⁹

For parameters where the industry and the FDA truly do not understand what works and why, this valuation approach may make sense, but even in areas where the relevant science is well understood, empiricism-based consistency still controls.¹⁹⁰ 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 the ingredient becomes soluble once released.¹⁹¹ Dissolution profiles help determine how fast the drug will enter the bloodstream.¹⁹² 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.¹⁹³ Any change, and every batch, must match the specified dissolution profile to be approved. The empiricism-based consistency approach for dissolution, however, 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).¹⁹⁴ For low-solubility drugs, the dissolution rate may be crucial to the drug's performance.¹⁹⁵ Thus, tight manufacturing controls, although costly, make sense for low-solubility drugs to ensure that dissolution profiles 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 varia-

¹⁸⁹ See DISSOLUTION, *supra* note 188, at 2 (“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.”).

¹⁹⁰ This system and its accompanying incentives may actively discourage the production of detailed drug knowledge, a question for future research.

¹⁹¹ See DISSOLUTION, *supra* note 188, at 1–2.

¹⁹² See *id.* Permeability through the walls of the gastrointestinal tract also significantly influences how quickly an oral dosage form enters the bloodstream. See *id.* at 4.

¹⁹³ *Id.* at 5, 8.

¹⁹⁴ See Yu, *supra* note 62, at 783. One commentator notes that “current 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.*” *Id.* (emphasis added). In contrast, under a more rational approach, highly soluble drugs could have wide acceptance limits, whereas low solubility drugs may need closer examination in dissolution testing. *Id.*

¹⁹⁵ See *id.* Regulators accept wider variation among highly soluble drugs; all of these drugs quickly react in the patient's system, so variations—even wide variations—among dissolution rates are not likely to affect how the drug reacts. See *id.* Conversely, for drugs that do not dissolve quickly, the point of solubility in the patient is often critical for the drug to be effective, and thus, regulators do not accept wide variation in these solubility rates. See *id.*

bility would affect drug efficacy,¹⁹⁶ tight manufacturing controls stand in the way of higher efficiency and other process innovations, 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 despite the fact that most firms do not optimize the initial manufacturing batches used for clinical trials for efficient high-quality, large-scale production.¹⁹⁷ Instead, most firms rush to produce clinical testing batches as fast as possible to speed drugs to market.¹⁹⁸ 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.¹⁹⁹ Low rates of clinical trial success also lead to decreased investments in developing robust manufacturing understanding because firms typically do not know early on whether a drug is likely to proceed to market.²⁰⁰ 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.²⁰¹

Overall, regulation stunts innovation in pharmaceutical manufacturing. In other industries, regulation is aimed at well-understood quality goals, and manufacturers can innovate to reach or surpass those goals efficiently.²⁰² In pharmaceutical manufacturing, however, the quality goals are defined observationally, on the basis of early, non-optimized manufacturing processes themselves. Thus, regulations encourage pharmaceutical manufacturing to maintain the status quo and prevent changes. Recent increased focus on quality regulations is likely to exacerbate the problem. The Department of Justice has stated that it plans to take an increased role in enforcing cGMP regulations.²⁰³ The FDA stated in parallel

¹⁹⁶ *See id.*

¹⁹⁷ *See* OPERATIONAL EXCELLENCE, *supra* note 56, at 80.

¹⁹⁸ *Id.*

¹⁹⁹ *See* REES, *supra* note 158, 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, *supra* note 64, at 80. Process development has been estimated to account for as much as 15–30% of R&D costs. Cox, *supra* note 78.

²⁰⁰ Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REVIEWS DRUG DISCOVERY 711, 711 (2004).

²⁰¹ AVELLANET, *supra* note 166, at 60. Under a Quality-by-Design (“QbD”) approach, discussed in Part III, manufacturing methods should ideally be largely in place by Phase II. *Id.*; *see infra* notes 358–374 and accompanying text.

²⁰² *See* Frimpong, *supra* note 109.

²⁰³ *Id.* Maame Ewusi-Mensah Frimpong, the U.S. Deputy Assistant Attorney General, 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.*

that it intended to make quality enforcement a major focus in 2013, even though the agency had already stepped-up enforcement of cGMP and quality regulations in the recent past.²⁰⁴ Increased enforcement is likely to encourage risk-averse adherence to old, approved processes rather than innovative change to newer, more robust methods.

Regulatory hurdles alone, however, cannot fully explain manufacturing stagnation because firms are able to overcome the tremendous regulatory hurdles for getting drugs initially approved. The lack of innovation in pharmaceutical manufacturing must also be attributed in large part to 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, which has been shaped by several Congressional acts, including the Hatch-Waxman Act,²⁰⁵ focuses on market exclusivity incentives for innovation in drug discovery and development. Foremost in innovation policy is the patent system, but the pseudo-patent system of FDA-administered statutory exclusivity is also used to augment and modify drug patents.²⁰⁶ These innovation incentives operate differently throughout the various stages of drug development. Patents, although available throughout the development process, are particularly prominent in protecting early investments.²⁰⁷ Patents also play a strong role after approval in staving off generic drug entry by preventing entry until the patents expire. Postapproval, patents also protect drug innovations through "evergreening," a set of tactics used by firms to extend effective patent protection on a drug.²⁰⁸ FDA regulatory exclusivity, on the other hand, applies only later in the drug development process, once the drug has already been approved and has entered the market.²⁰⁹

²⁰⁴ Hamburg, *supra* note 112.

²⁰⁵ Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28, & 35 U.S.C.).

²⁰⁶ See *Frequently Asked Questions on Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm>, archived at <http://perma.cc/74VG-2SNN> (last visited Feb. 13, 2014). Although FDA-administered market- or data-exclusivity are not typically considered intellectual property, this Article chooses to include them in this Section nonetheless because they function similarly to create exclusivity incentives for innovation, even though they lack some aspects of true intellectual property.

²⁰⁷ See E. W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 265–69 (1977).

²⁰⁸ See Eisenberg, *supra* note 15, at 354 & n.37; C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 327–28 (2012). Such strategies include obtaining patents on a drug's specific ingredients, an intermediate product, or on new uses for the product. Eisenberg, *supra* note 15, at 354.

²⁰⁹ Eisenberg, *supra* note 15, at 366.

In contrast to their role in drug discovery, patents and FDA regulatory exclusivity are not very effective at encouraging innovation in the field of pharmaceutical manufacturing. Because manufacturing process patents are hard to enforce, those patents involve an increased cost of disclosure coupled with a decreased exclusion benefit.²¹⁰ In addition, FDA regulatory exclusivity is unavailable for manufacturing innovations and thus plays no real role in incentivizing such innovation.²¹¹ As such, FDA regulatory exclusivity represents an opportunity for innovation policy.²¹²

Trade secrecy is significantly more important than patents and FDA regulatory exclusivity for manufacturing innovation.²¹³ Like patent or regulatory exclusivity, trade secrecy creates incentives for innovation by keeping others from copying the innovation and therefore allowing supracompetitive pricing.²¹⁴ Nevertheless, 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 also causes other problems. In particular, the unique aspects of trade secrecy—including its practical limitations, an unbounded timeframe, process-specificity, and limitations on personnel—make it structurally less capable of incentivizing pharmaceutical innovation.²¹⁵ In fact, the type of innovation most needed in drug manufacturing—innovations reflecting greater understanding and process knowledge—are particularly poorly suited to protection as trade secrets.²¹⁶

This Section shows that of the three main incentives for pharmaceutical innovation—patents, FDA market protection, and trade secrecy—only trade secre-

²¹⁰ See *infra* notes 235–247 and accompanying text (discussing how process patents' costs often outweigh their benefits).

²¹¹ See *infra* notes 270–283 and accompanying text (explaining that there is no FDA market exclusivity for manufacturing innovations).

²¹² See *infra* notes 419–425 and accompanying text (discussing the possibility of creating a regulatory exclusivity regime for manufacturing innovation).

²¹³ Cf. Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)* 34 tbl.2 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000), <http://www.nber.org/papers/w7552>, archived at <http://perma.cc/JW7A-EL2W>. According to a 1994 survey of the industry, pharmaceutical firms reported that 68% of process innovations could be effectively protected by secrecy, but only 36% by patents. *Id.* For products, the fractions were much closer at 54% and 50%, respectively. *Id.* at 33 tbl.1. This presumably refers to secrecy protection in the earlier stages of drug development, because drug details are public by the time a drug is marketed. See Anthony Arundel, *The Relative Effectiveness of Patents and Secrecy for Appropriation*, 30 RES. POL'Y 611, 613 (2001).

²¹⁴ See *infra* notes 223–283 and accompanying text (discussing patent and FDA market exclusivity in the pharmaceutical market).

²¹⁵ See *infra* notes 326–331 and accompanying text (noting the structural shortcomings of a trade secrecy regime).

²¹⁶ See *infra* notes 284–331 and accompanying text (analyzing trade secrets in pharmaceutical manufacturing).

cy seems to play a major role in encouraging innovation in pharmaceutical manufacturing.²¹⁷ But trade secrecy is flawed as an innovation motivator, at least in this context, because it lacks the temporal limitations of either the patent system or FDA market protection.²¹⁸ Trade secrecy also restricts socially useful disclosure, largely preventing cumulative innovation, which is central to major advances.²¹⁹ Trade secrecy is also least amenable to policy manipulation, as it has little to no government involvement. In sum, in the current system, there is scant intellectual property policy encouraging innovation in pharmaceutical manufacturing.

Subsection 1 describes patent law, including the shortcomings and benefits of process patents for manufacturing processes and the safe harbor provision of the Hatch-Waxman Act.²²⁰ Subsection 2 discusses FDA regulatory exclusivity and its failure to incentivize manufacturing innovation.²²¹ Finally, Subsection 3 analyzes trade secrets and how trade secrecy encourages innovation but suffers severe drawbacks as well.²²²

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 public disclosure of the knowledge created by the inventor.²²³ This disclosure is “the quid pro quo of the right to exclude.”²²⁴ 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.²²⁵ The patent monopoly lasts twenty years from the time of filing.²²⁶ During that time, the patentee has the right to exclude others from making, using, or selling the patented invention.²²⁷ The pharmaceutical industry is a clear

²¹⁷ See *infra* notes 223–331 and accompanying text.

²¹⁸ See *infra* notes 326–331 and accompanying text (explaining that innovation secrecy across the industry hinders continual innovation).

²¹⁹ See, e.g., Clarisa Long, *Patents and Cumulative Innovation*, 2 WASH. U. J.L. & POL’Y 229, 229–32 (2000); Scotchmer, *supra* note 31, at 32–33.

²²⁰ See *infra* notes 223–269 and accompanying text.

²²¹ See *infra* notes 270–283 and accompanying text.

²²² See *infra* notes 284–331 and accompanying text.

²²³ See *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int’l, Inc.*, 534 U.S. 124, 142 (2001).

²²⁴ *Id.* (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974)).

²²⁵ See Scotchmer, *supra* note 31, at 31. Trade secret law, to the contrary, neither requires nor allows disclosure of the innovation to the public. UNIF. TRADE SECRETS ACT § 1(4) (1985) (defining “trade secret” as information . . . that: (i) derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable . . . and (ii) is the subject of efforts . . . to maintain its secrecy”); see *infra* notes 284–331 and accompanying text (explaining that a lack of disclosure in a trade secrecy regime prevents continual innovation).

²²⁶ 35 U.S.C.A. § 154(a)(2) (West 2002 & Supp. 2013).

²²⁷ 35 U.S.C. § 271(a) (2006).

outlier in the extent to which patents help drive and shape R&D investment and innovation in developing new drugs.²²⁸ Both composition of matter patents on drugs and method patents, the latter of which cover the treatment uses of the drug, are important to drug innovation. Composition patents are more valuable because a patent on the drug's active ingredient allows the patentee to exclude others from making, selling, or using the drug for any use, even those uses not specifically envisioned by the patentee.²²⁹

In striking contrast, patents do little to stimulate manufacturing innovation. Patents on manufacturing processes,²³⁰ which cover using the processes in the United States or importing products made with the processes,²³¹ exist in the pharmaceutical industry but are less valuable and less common than other forms of pharmaceutical patents.²³² Patents fail to drive manufacturing innovation for

²²⁸ Bronwyn H. Hall & Dietmar Harhoff, *Recent Research on the Economics of Patents*, 4 ANN. REV. ECON. 541, 548 (2012) (describing a survey that found that patents effectively increase innovation primarily in the pharmaceutical industry); see also Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGMT. SCI. 173, 173, 175 tbl.1, 175–76 n.8 (1986) (noting that about 65% of pharmaceutical inventions would not have been introduced into the market absent patent protection, whereas no office equipment, motor vehicle, rubber, or textile innovations would have failed to be introduced); B.N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 545–56 (2008) (describing the pharmaceutical industry's unique dependence on patent protection to spur R&D investment).

²²⁹ Andrew Chadeayne, *Composition of Matter Claims*, CHADEAYNE, LLC, <http://inventingpatents.com/composition-matter-claims/>, archived at <http://perma.cc/6KF5-PDFQ> (last visited Feb. 15, 2014). 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. Patent No. 3,461,461 (filed Nov. 1, 1965), covered both the compound itself and a method of using it to treat high blood pressure. A later patent, U.S. Patent No. 4,139,619 (filed Aug. 19, 1977), 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 the FDA would not approve any generic version. See 21 U.S.C. § 355(a) (2012). Once the '461 patent expired, generic companies could apply to sell generic versions of Minoxidil to treat high blood pressure—which could then be prescribed for any purpose, including treating baldness. See *id.*

²³⁰ 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 Article 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.

²³¹ See 35 U.S.C. § 271(g). Merely using the process abroad does not infringe the patent. See *id.* Products made abroad using a U.S.-patented process may also be subject to an exclusion order by the U.S. International Trade Commission. See 19 U.S.C. § 1337(a)(1)(B)(ii) (2012).

²³² 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. SOC'Y 5, 23–37 (2002) (describing how process patent costs outweigh their benefits); see also Cohen et al., *supra* note 213, at 33–34 tbls. 1 & 2 (reporting 1994 survey results showing that pharmaceutical firms considered secrecy effective for 68% of process 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) (noting that “[i]nventors 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”).

two reasons: they have structural cost-benefit problems,²³³ and, more recently, they may be unavailable for certain important types of manufacturing innovation.²³⁴

a. Process Patents' High Costs and Low Benefits

Process patents' cost-benefit problems prevent these patents from meaningfully incentivizing manufacturing innovation. Process patents' costs are too high, and their benefits are too low. The costs are too high because manufacturers do not want to give up their competitive advantage by publicly disclosing their processes.²³⁵ 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.

Process patents' benefits are low because they are very hard to enforce.²³⁶ First, process patents are usually easier to invent around than product patents because infringing a process patent requires performing every step of the process.²³⁷ Thus, competitors have more opportunities for variation to escape patent coverage.²³⁸ In addition, determining infringement can be particularly challenging because "no one outside the potential infringer knows how the product was made."²³⁹ 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).²⁴⁰

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

²³³ See *infra* notes 235–247 and accompanying text.

²³⁴ See *infra* notes 248–269 and accompanying text.

²³⁵ See Girish Malhotra, *Are Patents a Double-edged Sword? Perspective Matters.*, PROFITABILITY THROUGH SIMPLICITY (Feb. 8, 2011, 7:37 AM), <http://pharmaceuticalscoatings.blogspot.com/2011/02/are-patents-double-edged-sword.html>, archived at <http://perma.cc/U56G-UFB3>.

²³⁶ See Lewis & Cody, *supra* note 232, at 23–37 (discussing the difficulties of bringing process patent suits, and in particular, noting that courts have imposed Rule 11 sanctions against attorneys who fail to take reasonable steps to determine infringement and laborious investigative steps to support process infringement lawsuits).

²³⁷ See *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1305–07 (Fed. Cir. 2012).

²³⁸ *Id.* See generally Cohen et al., *supra* note 213, at 47 fig.6 (reporting that in a 1994 cross-industry survey, the ability to invent around a patent was one of the most important reasons that firms chose not to patent demonstrably novel innovations).

²³⁹ Lewis & Cody, *supra* note 232, at 7. Identifying international infringement may be particularly challenging. *Id.* at 9.

²⁴⁰ *Cf.* *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314–15 (Fed. Cir. 2011) (discussing a suit involving a product-specific patent and the hurdles to uncovering such processes).

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.”²⁴¹ Nonetheless, 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 may differ because manufacturing methods are unusually central for biologics.²⁴² Even more so than for small-molecule drugs, the manufacturing complexity and development costs for biologics can serve as a potent barrier to entry, keeping competitors off the market.²⁴³ 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 patents particularly unattractive. Despite the risks of disclosure, some firms pursue process patents.²⁴⁴ For example, AbbVie has around 200 manufacturing patents protecting the production of Humira, a biologic with over \$10 billion in yearly sales used to treat arthritis,²⁴⁵ and intends to use them to

²⁴¹ 35 U.S.C. § 295 (2006); see *Creative Compounds*, 651 F.3d at 1315. “Substantial likelihood” is described in one Senate Judiciary Committee 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.” See JOE BIDEN, SENATE JUDICIARY COMM., REPORT ON THE PROCESS PATENTS AMENDMENTS ACT OF 1989, S. REP. NO. 100-83, at 45 (1987). If both conditions found in § 295 are met, the burden shifts to the accused infringer to prove noninfringement. *Creative Compounds*, 651 F.3d at 1314–15 (“Because 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.” (citing Lewis & Cody, *supra* note 232, at 22–23)). Although § 295 applies to both foreign and domestic manufacturing, domestic manufacturers can likely determine the process used. See S. REP. NO. 100-83, at 45. According to the Senate Judiciary Committee report:

The 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.

Id.

²⁴² A comprehensive analysis of manufacturing patent strategy differences must await future work. An additional important element in biologic patent strategy comes from the differences in patent-challenge procedures for small-molecule drugs and for biologics. For a detailed explanation, see generally Michael P. Dougherty, *The New Follow-On Biologics Law: A Section by Section Analysis of the Patent Litigation Provisions in the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 231 (2010).

²⁴³ See *supra* notes 55–59 and accompanying text (discussing the complexities of biologics manufacturing).

²⁴⁴ This may be especially true for previously known biologics, which are for ineligible patent protection as compositions of matter. Manufacturing process patents provide at least some protection.

²⁴⁵ Christopher Weaver et al., *Biotech Drugs Still Won't Copy*, WALL ST. J. (Feb. 26, 2013, 7:25 PM), <http://online.wsj.com/news/articles/SB1000142412788732386430457831811144984632>.

extend its market exclusivity period past the 2016 expiration of Humira's primary compound patents.²⁴⁶

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.²⁴⁷ Firms that do not pursue process patents apparently value the cost of the disclosure as more significant than the speculative benefits to be gained from enforcing process patents.

b. The Safe Harbor of 35 U.S.C. § 271(e)(1)

Despite the structural problems, at least some manufacturing process patents are worth pursuing. But many of these patents have recently been made less valuable because of a likely unintended quirk of the Hatch-Waxman Act, which essentially renders unenforceable a class of patents covering techniques central to modernizing manufacturing.²⁴⁸

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."²⁴⁹ The safe harbor was enacted to allow generic drug companies (and now, biosimilar companies) to develop products, along with the required comparability and safety information, before the expiration of the pioneer company's patent.²⁵⁰ The safe harbor allows generic firms to win approval and be ready to market the drug as soon as the pioneer's patents (or market exclusivity periods) expire.

²⁴⁶ *Id.*

²⁴⁷ *See supra* notes 235–246 and accompanying text. 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.

²⁴⁸ *See* 35 U.S.C. § 271(e)(1) (2006) (providing that there is no patent infringement for utilization of a manufacturing process done "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").

²⁴⁹ *Id.*

²⁵⁰ *See id.*; *Momenta Pharm., Inc. v. Amphastar Pharm., Inc.*, 686 F.3d 1348, 1354–56 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 2854 (2013). "Biosimilars" are products that are highly similar to a biological product that has already received FDA approval. *Biosimilars*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>, archived at <http://perma.cc/D8HY-5DZ4> (last visited Feb. 13, 2014).

The techniques potentially implicated by the safe harbor are central to modern manufacturing. These techniques are especially important for biosimilars because biosimilars require extensive analytical testing to demonstrate biosimilarity.²⁵¹ To the extent that patent protection for such techniques could provide innovation incentives, those incentives were recently weakened.

In 2012, in *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, the U.S. Court of Appeals for the Federal Circuit vacated a preliminary injunction against a generic company because the generic's use of a pioneer's patented technology to prepare submissions to the FDA before the patent's expiration fell within the Hatch-Waxman's safe harbor provision.²⁵² *Momenta* involved the making of 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.²⁵³ The FDA established five analytically complex and technically challenging "standards for identity" to establish that "generic enoxaparin has the 'same' active ingredient as Lovenox."²⁵⁴ *Momenta*²⁵⁵ and Amphastar both filed ANDAs for generic versions of enoxaparin.²⁵⁶ *Momenta's* application was approved first²⁵⁷—an approval worth over \$1 billion annually when *Momenta's* was the only approved generic.²⁵⁸

Two days after Amphastar's ANDA was approved, *Momenta* sued Amphastar for infringing its patent, which claimed "methods for analyzing heterogeneous populations of sulfated polysaccharides, e.g. heparin [and enoxaparin]."²⁵⁹ Such methods were largely described in and required by one of the FDA's "standards for identity."²⁶⁰ *Momenta* alleged that Amphastar was infringing its patent by using the claimed method to show that each commercial batch

²⁵¹ U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 8–12 (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>, archived at <http://perma.cc/3ESZ-QGY Y> (providing guidance and outlining the specific and somewhat arduous process of demonstrating biosimilarity).

²⁵² 686 F.3d at 1349–52, 1361.

²⁵³ *Id.* at 1349–50.

²⁵⁴ *Id.* at 1350.

²⁵⁵ *Momenta* partnered with Sandoz, Inc., (collectively "*Momenta*") for this joint venture. *Id.* at 1351.

²⁵⁶ *Id.*

²⁵⁷ *Id.*

²⁵⁸ *Id.*

²⁵⁹ U.S. Patent No. 7,575,886 col. 4 II. 53–55 (filed Mar. 11, 2003); see *Momenta Pharm.*, 686 F.3d at 1351.

²⁶⁰ *Momenta Pharm.*, 686 F.3d at 1350–52. See generally Letter from Douglas Throckmorton, Deputy Dir., Ctr. for Drug Evaluation and Research, to Peter O. Safir and Scott L. Cunningham, Aventis Pharmaceuticals, Inc. 17–18 (July 23, 2010), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf>, archived at <http://perma.cc/M5HJ-XAEZ> (applying the FDA's five-part test for identity and denying most of Aventis's petition that the FDA deny approval of any generic versions of Lovenox).

of its generic enoxaparin was bioequivalent to Lovenox.²⁶¹ The district court preliminarily enjoined Amphastar from using the technology.²⁶²

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.²⁶³ In fact, the information need never be submitted to the FDA, as long as it is “reasonably related” to such a submission.²⁶⁴ 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.²⁶⁵ The court held that under these regulations, Amphastar’s use of the batch testing data in this case was “reasonably related” to a submission and therefore fell under the safe harbor.²⁶⁶

Modern manufacturing will require increasing amounts of in-line testing, examination of complex product characteristics, and analytical “fingerprinting” techniques.²⁶⁷ These methods are neither simple nor cheap to develop and are relatively easy to copy once known, so they are paradigm cases for intellectual property. But the current legal regime removes both major policy sources of innovation incentives for developing such techniques. First, the 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 a patent-protected monopoly. A vigorous dissent from Chief Judge Randall Rader recognized the 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.”²⁶⁸

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 the FDA necessary for approval, with the goal of making it more difficult to copy

²⁶¹ *Momenta Pharm.*, 686 F.3d at 1352.

²⁶² *Momenta Pharm., Inc. v. Amphastar Pharm., Inc.*, 882 F. Supp. 2d 184, 199 (D. Mass. 2011).

²⁶³ *Momenta Pharm.*, 686 F.3d at 1354, 1361.

²⁶⁴ *Id.* at 1357.

²⁶⁵ 21 C.F.R. § 211.180(c) (2013); see *Momenta Pharm.*, 686 F.3d at 1357.

²⁶⁶ *Momenta Pharm.*, 686 F.3d at 1353, 1358. The court distinguished its 2011 decision *Classen Immunotherapies, Inc. v. Biogen Idec*, which held that the safe harbor does not extend to “information that may be routinely reported to the FDA, long after marketing approval has been obtained,” 659 F.3d 1057, 1070 (Fed. Cir. 2011), 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 Pharm.*, 686 F.3d at 1353, 1358. The court also held that the FDA requires Amphastar to use the patented method to batch-test its enoxaparin for conformity with the identity standards. *Id.* at 1361.

²⁶⁷ See Yves Roggo et al., *A Review of Near Infrared Spectroscopy and Chemometrics in Pharmaceutical Technologies*, 44 J. PHARMACEUTICAL & BIOMEDICAL ANALYSIS 683, 687 (2007).

²⁶⁸ *Momenta Pharm.*, 686 F.3d at 1376 (Rader, J., dissenting).

the novel techniques.²⁶⁹ These effects hurt 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 the patents' basic structural problems of 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 the FDA. For drug products, the FDA is statutorily authorized to grant periods of market protection—market or data exclusivity—parallel to the patent system.²⁷⁰ This protection can be granted as a reward for winning approval for a new chemical entity,²⁷¹ a treatment for a rare disease,²⁷² or a new indication.²⁷³ Protection can also be granted for conducting pediatric studies.²⁷⁴ Since 2010, biologics have similar periods of market protection.²⁷⁵ In addition to pioneers, protection is also available for some first-approved generics²⁷⁶ or interchangeable-

²⁶⁹ Judging *Momenta* on the merits and prognosticating its effects on biosimilar development are both outside the scope of this Article.

²⁷⁰ See 21 U.S.C. § 355(c)(3)(E) (2012). This exclusivity can be market exclusivity, in which the 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 innovation incentive—is the same. Accordingly, this Article conflates the two forms under the term “market protection.”

²⁷¹ See *id.* § 355(j)(5)(F)(ii) (granting five years of market exclusivity for new chemical entities not previously approved for any indication by the FDA).

²⁷² See 21 U.S.C. § 360cc(a) (2012) (granting seven years of market exclusivity for drugs targeting rare diseases that affect fewer than 200,000 patients in the United States).

²⁷³ See *id.* § 355(j)(5)(F)(iii) (granting three years for product changes requiring new clinical trials, including switching to over-the-counter status or adding a new dosage form).

²⁷⁴ See *id.* § 355a(b) (granting six months of additional exclusivity for conducting pediatric trials, which need not be limited to pediatric uses).

²⁷⁵ See 42 U.S.C.A. § 262(k)(7) (West 2011 & Supp. 2013) (granting four years of market exclusivity and an additional eight years of data exclusivity). The twelve-year exclusivity period granted by § 262 does not apply to relatively minor changes to an approved biologic. *Id.* Furthermore, an additional six months may be added based on the performance of pediatric studies. *Id.* § 262(m).

²⁷⁶ 21 U.S.C. § 355(j)(5)(B)(iv).

ble biosimilars.²⁷⁷ This “pseudo-patent” market protection, when in force, may even be more valuable than a patent because it is government-enforced and essentially unchallengeable. Conversely, patents require expensive private enforcement and are subject to legal challenge.²⁷⁸ FDA market exclusivity also has various other benefits for pioneer companies.²⁷⁹

The FDA’s market protection regime creates incentives to not only discover new drugs but also to generate valuable information about drug efficacy through expensive and risky clinical trials.²⁸⁰ This information is socially valuable but costly for firms to generate, and firms are unable to capture much of the information’s value.²⁸¹ The FDA promotes information creation through its initial market approval process, where approval is indication specific, and through its prohibition on industry promotion of off-label uses without adequate supporting clinical information.²⁸²

Despite the power of the FDA’s innovation incentives, however, the incentives focus exclusively on the process of bringing individual drugs to market. Even those provisions that take effect after the initial market approval (for example, exclusivity for changes requiring clinical trials or for pediatric trials) focus on preapproval-type information and activities, such as verifying the safety and efficacy of the drug. FDA exclusivity incentives do not exist for manufacturing innovation. Rather, the only FDA-mediated manufacturing incentives appear to be the ability to avoid the costs of quality failures and plant shutdowns due to the FDA’s regulatory oversight.²⁸³

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 or

²⁷⁷ See 42 U.S.C. § 262(k)(6) (granting exclusivity for twelve to forty-two months, during which no other interchangeable product can enter the market).

²⁷⁸ Eisenberg, *supra* note 15, at 364–66.

²⁷⁹ *Id.* at 362–66.

²⁸⁰ *Id.* at 370.

²⁸¹ See *id.*

²⁸² *Id.* The FDA’s ability to prohibit off-label marketing has come under serious question. *Cf. Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011). In the 2011 U.S. Supreme Court case *Sorrell v. IMS Health, Inc.*, the Court held that pharmaceutical marketing is “a form of expression protected by the Free Speech Clause of the First Amendment.” *Id.* And in 2012, the Second Circuit held that the 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).

²⁸³ See generally *supra* notes 3–9 and accompanying text (discussing the costs of recent contamination events).

exclusivity incentive for pharmaceutical manufacturing.²⁸⁴ Trade secret law provides protection from misappropriation of information that is reasonably kept secret and derives value from its secrecy.²⁸⁵ Trade secrets play a bigger role in protecting manufacturing processes for at least three reasons. First, enforcing manufacturing process patents is difficult, whereas the effectiveness of trade secrets—as long as they can be kept secret—does not depend on monitoring other firms' activities.²⁸⁶ 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 predetermined lifespan; they may continue indefinitely. Given these advantages, trade secrets have long been important to protecting manufacturing processes, and are increasingly so.²⁸⁷ Although reported cases are relatively rare, they provide illustrative examples of the possible roles trade secrets can play in manufacturing innovation.²⁸⁸

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 that change market contours. These scenarios are described below in Subsection 3.a.²⁸⁹ Like manufacturing patents, however, trade secrets can be hard to enforce, though in different ways. For example, the same secrecy that keeps the innovator company's intellectual property secret can render the misappropriator's use of the secret difficult to detect. Similarly, this secrecy can make it hard to determine whether the second firm in fact misappropriated the trade secret or just discovered it independently. These difficulties are described below in Subsection 3.b.²⁹⁰ And even if trade secrets provide some functional incentive to innovate, they create other difficulties both for the innovation process within a

²⁸⁴ Telephone Interview with Geoffrey Levitt, Senior Vice President & Assoc. Gen. Counsel, Pfizer (Nov. 29, 2012); see *supra* notes 223–283 and accompanying text (discussing the shortcomings of patent and FDA market exclusivity in promoting manufacturing innovation).

²⁸⁵ See UNIF. TRADE SECRETS ACT § 1(4) (1985).

²⁸⁶ See John Avellanet, *Securing Intellectual Property from the Inside Out*, in BEST PRACTICES IN BIOTECHNOLOGY BUSINESS DEVELOPMENT: VALUATION, LICENSING, CASH FLOW, PHARMACOECONOMICS, MARKET SELECTION, COMMUNICATION, AND INTELLECTUAL PROPERTY 37, 37 (Yali Friedman ed., 2008).

²⁸⁷ Robert Graham Gibbons & Bryan J. Vogel, *The Increasing Importance of Trade Secret Protection in the Biotechnology, Pharmaceutical and Medical Device Fields*, 89 J. PAT. & TRADEMARK OFF. SOC'Y 261, 262 (2007).

²⁸⁸ There are relatively few reported cases about pharmaceutical trade secrets. It is unclear whether this comes from a low frequency of trade secrets, trade secret misappropriations, litigation of discovered misappropriations to judgment, or some combination.

²⁸⁹ See *infra* notes 292–309 and accompanying text.

²⁹⁰ See *infra* notes 310–325 and accompanying text.

firm and for the spread of social benefits from innovation. These structural weaknesses of a trade secret regime are discussed below in Subsection 3.c.²⁹¹

a. Monopoly Maintenance by Excluding Competitors

Trade secrets may provide innovators with an indefinite monopoly, thus allowing pioneers to earn extensive supracompetitive revenues. One case that illuminates both the indefinite duration of trade secrets and the difficulty of replicating essential manufacturing techniques is the drug Premarin. In 2003, in *Wyeth v. Natural Biologics*, the U.S. District Court for the District of Minnesota permanently enjoined Natural Biologics from using Wyeth's unpatented estrogen removal process (the "Brandon Process") to make generic Premarin because Natural Biologics misappropriated the process in violation of Minnesota's Uniform Trade Secrets Act.²⁹² Wyeth manufactures Premarin for the treatment of symptoms associated with menopause and sells over \$1 billion in Premarin yearly.²⁹³

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 1942.²⁹⁴ Synthetic estrogens exist, but are not FDA-approved as generic substitutes for naturally derived Premarin.²⁹⁵ No competitor has entered the market, however, primarily because of the difficulty in extracting the estrogens.²⁹⁶

Wyeth extracts and purifies the estrogens at a plant in Brandon, Manitoba, using the Brandon Process that Wyeth claimed as a trade secret.²⁹⁷ Wyeth obtained several early patents on methods connected with estrogen extraction research.²⁹⁸ These patents, however, provided insufficient information to recreate

²⁹¹ See *infra* notes 326–331 and accompanying text.

²⁹² *Wyeth v. Natural Biologics, Inc.*, No. Civ. 98-2469, 2003 WL 22282371, at *18–19, *27–29 (D. Minn. Oct. 2, 2003), *aff'd*, 395 F.3d 897 (8th Cir. 2005). See generally MINN. STAT. § 325C.01 (2013).

²⁹³ *Id.* at *1, *2.

²⁹⁴ *Id.* at *1. Premarin was approved as a drug under the Food Drug, and Cosmetics Act, rather than as a biologic under the Public Health Services Act, which had not yet been enacted. Accordingly, generic versions could be approved via the ANDA process.

²⁹⁵ Press Release, U.S. Dep't of Health & Human Servs., U.S. Food & Drug Admin., FDA Statement on Generic Premarin (May 5, 1997), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169045.htm>, archived at <http://perma.cc/ZJ7P-STXX>. The FDA decided not to approve synthetic estrogens as generic Premarin because the role of the various estrogens found in Premarin are not fully understood. See *id.* Premarin was approved before requirements for comprehensive analysis became a prerequisite for marketing approval. See *id.*

²⁹⁶ See *Wyeth*, 2003 WL 22282371, at *1.

²⁹⁷ *Id.* at *2.

²⁹⁸ *Id.*

the Brandon Process, which is unpatented.²⁹⁹ Wyeth took several measures to ensure the secrecy of the Brandon Process.³⁰⁰ 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.³⁰¹

Several major companies attempted to duplicate Wyeth's success by extracting estrogens from PMU.³⁰² All failed.³⁰³ 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.³⁰⁴ 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 the Brandon plant's waste chemicals.³⁰⁵ On learning of Natural Biologics's 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.³⁰⁶ The court permanently enjoined Natural Biologics from researching or developing any methods for extracting estrogens from urine or manufacturing any such estrogens.³⁰⁷

Wyeth's trade secret of the precise manufacturing technique for Premarin illustrates 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.³⁰⁸ But here, although Wyeth was granted several patents on Premarin—including patents specifically on techniques for extracting estrogens from urine—those patents did not disclose enough information for other firms to recreate Premarin once the patents had expired.³⁰⁹ Accordingly, Wyeth was able to maintain its monopoly pricing for far longer than the term envisioned by the patent bargain—over seventy years—causing deadweight loss to society well past

²⁹⁹ *Id.* Wyeth's estrogen extraction patents included, among others, U.S. Patent No. 2,429,398 (filed May 23, 1944); U.S. Patent No. 2,551,205 (filed Oct. 1, 1947); U.S. Patent No. 2,696,265 (filed Dec. 11, 1948); and U.S. Patent No. 2,834,712 (filed May 27, 1953). *Id.* The '712 patent expired in May 1975. *Id.*

³⁰⁰ *Id.* at *3–5.

³⁰¹ *Id.* at *3.

³⁰² *Id.* at *9.

³⁰³ *Id.*

³⁰⁴ *Id.* at *6–10.

³⁰⁵ *Id.* at *5–6.

³⁰⁶ *Id.* at *18, *21.

³⁰⁷ *Id.* at *25–28.

³⁰⁸ Hall & Harhoff, *supra* note 228, at 542. *See generally supra* notes 223–225 and accompanying text (discussing patent disclosure requirements).

³⁰⁹ *See Wyeth*, 2003 WL 22282371, at *1.

the time needed to recoup development costs. Finally, whatever the secret manufacturing method is for making Premarin, that method must lack new innovation. The 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, although a monopoly protected by trade secrecy is certainly a potent incentive for some manufacturing innovation, the secrecy also impedes other innovation.

b. Non-Monopoly Incentives and Enforcement Challenges

Not all trade secrets completely enforce a monopoly. One case involving veterinary penicillin³¹⁰ demonstrates the competitive cost advantage incentives of an innovative manufacturing technique, but also illustrates the challenges of enforcing trade secrets, which limits trade secrecy's use as innovation drivers.

In 2003, in *Norbrook Laboratories Ltd. v. G.C. Hanford Manufacturing Co.*, the U.S. District Court for the Northern District of New York held that Hanford misappropriated Norbrook's manufacturing method for producing veterinary penicillin and permanently enjoined Hanford from using the method.³¹¹ Norbrook developed a method of manufacturing veterinary penicillin by conducting the final manufacturing reaction *in situ* without having to dry the intermediate product.³¹² 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, but the raw materials for the novel method cost only \$9 per kilogram.³¹³ The new method was sufficiently different that the FDA deemed it a radical shift from the normal method recognized by the USP and required that the method be separately approved.³¹⁴ Eventually, Norbrook persuaded both the USP and the FDA to approve its *in situ* method.³¹⁵ Af-

³¹⁰ *Norbrook Labs. Ltd. v. G.C. Hanford Mfg. Co.*, 297 F. Supp. 2d 463 (N.D.N.Y. 2003).

³¹¹ *Id.* at 483–90, 492–93.

³¹² *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. *Id.* at 468. 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. *Id.* 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. *Id.* at 468–69. Cost savings come from avoiding drying time and avoiding the need for a third-party supplier of the intermediate product. *Id.*

³¹³ *Id.* at 469.

³¹⁴ *See id.* at 471.

³¹⁵ *Id.*

ter approval, the “significant cost advantages” from the new process allowed Norbrook to acquire most of its competitor Hanford’s customers and make significant inroads into the U.S. market for veterinary penicillin.³¹⁶

The process was so market-changing that Hanford hired Dr. Quinn, the scientist who had invented Norbrook’s procedure, and who had subsequently left Norbrook and signed a confidentiality agreement, and induced him to share Norbrook’s trade secret manufacturing innovation.³¹⁷ Once Hanford had acquired the details of Norbrook’s *in situ* manufacturing process, Hanford was able to implement the process rapidly, without any major changes, and received FDA approval almost immediately.³¹⁸

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.³¹⁹ In discovery, Norbrook uncovered the contacts between Hanford and Dr. Quinn during a deposition of Hanford’s CEO.³²⁰ Norbrook made a Freedom of Information Act (“FOIA”) request to the FDA, asking whether Hanford had sought approval to modify its penicillin manufacturing process since Hanford had hired Dr. Quinn.³²¹ The FDA provided a heavily redacted document.³²² Norbrook investigated further and eventually concluded that Hanford had applied for approval to change from conventional to *in situ* manufacturing.³²³ Thereafter, Norbrook sent a cease-and-desist letter to Hanford and then initiated its suit for misappropriation of trade secrets.³²⁴ In the end, the district court found misappropriation of trade secrets and preliminarily enjoined Hanford from using or publishing Norbrook’s *in situ* process.³²⁵

Norbrook’s trade secret thus allows it a significant and continuing market advantage, acting as an incentive for the earlier innovation. This case, however,

³¹⁶ *Id.* at 473.

³¹⁷ *Id.* at 474–79.

³¹⁸ *Id.* at 477–79.

³¹⁹ *Id.* at 472. 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 469, 472. Norbrook had also separately sued Dr. Quinn twice for other breaches of his contractual confidentiality obligations; neither breach was related to the *in situ* technology. *Id.*

³²⁰ *Id.* at 469, 472.

³²¹ *Id.* at 469. See generally Freedom of Information Act, 5 U.S.C. § 552 (2012) (requiring agencies to make available certain information to the public); *id.* § 552(a)(3)(A) (creating a formal request-and-response process); Margaret B. Kwoka, *Deferring to Secrecy*, 54 B.C. L. REV. 185, 196–200 (2013) (discussing FOIA).

³²² *Norbrook Labs*, 297 F. Supp. 2d at 469

³²³ *Id.*

³²⁴ *Id.*

³²⁵ *Id.* at 489–94.

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. Even well-functioning trade secrets, however, have serious problems when viewed from the standpoint of innovation policy.³²⁶ First, as long as secrecy is maintained, which may be indefinitely, no other firms—competitors or not—can benefit from the innovation, and society cannot benefit from any cumulative innovation based on the secret.³²⁷ A tremendous amount of innovation is cumulative, and a large portion of cumulative innovation is made by firms other than the first innovator.³²⁸

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.³²⁹ 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 cannot easily be misappropriated.³³⁰ Thus, very few people even within the firm can build on the innovation.

³²⁶ For a more thorough treatment of problems with trade secrecy as an innovation regime, see Robert G. Bone, *A New Look at Trade Secret Law: Doctrine in Search of Justification*, 86 CALIF. L. REV. 241, 264–70 (1998), which argues that trade secrets' costs cannot be justified because innovations are already adequately protected by patent, copyright, trademark, contract, and criminal law. *Contra* Mark A. Lemley, *The Surprising Virtues of Treating Trade Secrets as IP Rights*, 61 STAN. L. REV. 311, 328–32 (2008) (addressing Bone's article and arguing that trade secrets should be understood as IP rights because they act like patents and copyrights by encouraging innovation through exclusivity and the promise of supracompetitive profits).

³²⁷ See Nisvan Erkal, *The Decision to Patent, Cumulative Innovation, and Optimal Policy*, 23 INT'L J. INDUS. ORG. 535, 536–38 (2005).

³²⁸ See Scotchmer, *supra* note 31, at 29–32.

³²⁹ *Cf. Wyeth*, 2003 WL 22282371, at *3 (noting that the manufacturing process at issue in *Wyeth* was in use since 1966 but was not written down until 1979).

³³⁰ See AVELLANET, *supra* note 166, at 149. According to one set of recommendations regarding best practices for trade secret-related standard operating procedures ("SOPs"):

One way to compartmentalize and separate information is to eliminate any intellectual property that reveals step-by-step details of a process. For a formulation, firms might leave out specific measurements, relying upon training and separate ingredients list that is tightly controlled. The key is to avoid making it so easy that someone just needs to take one document to obtain critical intellectual property. The more records a person has to search through and assemble, the greater his or her chances are of getting caught. Biotechnology firms will want to be especially careful with trade secret processes. It is

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. Furthermore, some innovations are inherently hard to reward through trade secrecy. For instance, because trade secrets are harder to license, a trade secret regime provides lower incentives for innovations that require widespread use by multiple actors (e.g., network effects) to create value for the innovator. These types of broad innovations—like sampling techniques, quality analysis, or process workflow—are key to large-scale improvements in pharmaceutical manufacturing. Unfortunately, they also fit poorly with an intellectual property regime dominated by trade secrets.

Despite trade secrets' limits, they 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. Trade secrets, however, 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 means that companies regularly fail to surmount the regulatory hurdles to innovation. The innovation deficiency of pharmaceutical manufacturing, with its major attendant problems, is the unfortunate result.³³¹

absolutely essential to split such processes over multiple SOPs, leaving out critical parameters whenever possible, referring a reader to other, more tightly controlled documents.

Id.

³³¹ Although this Article describes mostly brand-name drug companies, generic companies face the same central problem of juxtaposed low intellectual property incentives and high regulatory barriers to change. Setting aside the 180-day period of exclusivity sometimes available for the first generic to enter the market, U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: 180-DAY GENERIC DRUG EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 1 (1998), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079342.pdf>, *archived at* <http://perma.cc/NWT2-5HD6>, generics also face timing pressures when entering the market. Because the price and market share of an individual generic drops rapidly as more generics enter the market, entering the market quickly is quite valuable. Thus, generics face similar incentives to make ANDA approval as quick as possible. Other regulatory barriers, including procedural hurdles, substantive lock-in, and de facto standards, all also apply to generics. And although the relatively low margins of generic manufacturing may increase the relative salience of manufacturing cost-savings, generics still face the absence of any supramarket incentives for innovation.

III. NEW DIRECTIONS FOR MANUFACTURING INNOVATION POLICY

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 benefit the industry and the health care system as a whole. The drug industry innovates in drug discovery and development, but other industries innovate in manufacturing. These comparators suggest that drug manufacturing could be a successful target of innovation policy.³³²

The complexity of the problem, arising from interacting intellectual property and regulatory structures, forestalls a single simple solution. The unique role that regulatory oversight plays in creating hurdles to manufacturing innovation, and the contrary role oversight 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.³³³ Some potential changes focus solely on regulatory hurdles. Others, however, suggest ways that regulation could mediate and change innovation incentives. Regulation could shape these incentives to drive manufacturing innovation more effectively by encouraging firms to surmount what regulatory hurdles are necessary.³³⁴ This type of cooperative approach works well in drug discovery and development and also offers possibilities for innovative manufacturing. One final

³³² These proposed policy changes, although addressing only the domestic market, also have international implications. Drug manufacturing takes place in a global marketplace, but an exhaustive comparative account of global pharmaceutical manufacturing oversight is far beyond the scope of this Article. North America, however, comprised 41.8% of the global pharmaceutical market in 2011. EUROPEAN FED'N OF PHARM. INDUS. & ASS'NS, *THE PHARMACEUTICAL INDUSTRY IN FIGURES: KEY DATA 2012*, at 4 (2012), available at http://www.efpia.eu/uploads/Modules/Documents/efpia_figures_2012_final-20120622-003-en-v1.pdf, archived at <http://perma.cc/D5T3-E2YX>. And the FDA regulates drug manufacturers in 190 countries producing drugs for the U.S. market. See *FDA's International Posts: Improving the Safety of Imported Food and Medical Products*, U.S. FOOD & DRUG ADMIN., <http://test.fda.gov/ForConsumers/ConsumerUpdates/ucm185769.htm>, archived at <http://perma.cc/C8X6-6934> (last updated Mar. 31, 2010). Furthermore, other regulatory regimes are broadly similar and similarly inhibit manufacturing innovation. Telephone Interview with Prabir Basu, President, Pharma Mfg. (May 6, 2013); Telephone Interview with Hedley Rees, Managing Consultant, PharmaFlow, Ltd. (Mar. 8, 2013). Domestic solutions have the potential for international implications if innovation is developed here and then spreads; that innovation can be regulatory (i.e., the new structures being proposed here), or manufacturing (i.e., the intended results of those new structures). This is particularly true because many markets outside the EU and Japan accept approval of manufacturing changes by the FDA without the need for independent review.

³³³ 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.

³³⁴ 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 as well. This shift 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.

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.³³⁵

Section A of this Part addresses possible changes to the regulatory structure to encourage innovation.³³⁶ Section B of this Part then discusses how regulations themselves may be used to incentivize manufacturing innovation.³³⁷ Finally, Section C discusses the market's lack of quality indicators and quality competition and suggests methods for coping with these market shortcomings.³³⁸

A. Changes to Regulatory Structures

Reforming the oversight structure is one mechanism for improving innovation because regulatory oversight imposes both procedural and substantive hurdles to manufacturing 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.³³⁹ Second, the FDA could improve innovation by reducing its substantive barriers.³⁴⁰ One such effort that is slowly progressing is the FDA's Quality by Design ("QbD") initiative.³⁴¹ Third, the FDA could provide increased regulatory flexibility, thus loosening procedural barriers to innovative change.³⁴² Fourth, the FDA could change industry development incentives by requiring deeper manufacturing understanding earlier in the development process.³⁴³ Fifth and finally, the FDA could provide an independent validation pathway for new technologies, separate from the NDA process.³⁴⁴

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. Pro-

³³⁵ A rich literature describes these other innovation incentives. For an excellent overview of the literature and a taxonomy of innovation incentives, see generally Daniel Jacob Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303 (2013). Once the central problem of mismatched incentives and regulatory barriers is noted, the choice of solutions—and of particular forms of incentives—can be varied according to the desired effects. Some potential prize solutions might involve tailoring the reward to a fraction of industry-wide cost savings, which would encourage firms to share and teach their innovations; such a scheme would be administratively challenging to implement, however.

³³⁶ See *infra* notes 339–403 and accompanying text.

³³⁷ See *infra* notes 404–425 and accompanying text.

³³⁸ See *infra* notes 426–444 and accompanying text.

³³⁹ See *infra* notes 345–357 and accompanying text.

³⁴⁰ See *infra* notes 358–374 and accompanying text.

³⁴¹ See *infra* notes 375–384 and accompanying text.

³⁴² See *infra* notes 375–388 and accompanying text.

³⁴³ See *infra* notes 389–397 and accompanying text.

³⁴⁴ See *infra* notes 398–403 and accompanying text.

ponents of this approach suggest that the FDA be removed from the role of regulating drug development, manufacturing, and marketing.³⁴⁵ FDA removal could result in the absence of any oversight at all. Before the FDA existed, however, the industry suffered enormous quality problems, so a complete removal of all regulation would be unlikely.³⁴⁶ Instead, oversight would likely fall to the states or to the market and tort systems.³⁴⁷

Removing the FDA's regulatory power and federal preemption of drug regulation would allow states to regulate drug manufacturing.³⁴⁸ State oversight, however, would likely face fierce opposition from drug manufacturers, who already must navigate the challenge of complying with different national drug regulation regimes in multiple countries.³⁴⁹ If state regulations were to replace the FDA and federal oversight, then the problems 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 the FDA, could certify that marketed drugs are safe and effective, as is done today for certain consumer goods.³⁵⁰ Compliance with private certification could either be left entirely to market mechanisms to establish or could be federally mandated.³⁵¹ Drug manufacturers would submit to an inspection regime run by private certification bodies, which

³⁴⁵ See N.D. CAMPBELL, NAT'L CTR. FOR POL'Y ANALYSIS, MAKING DRUGS SAFE AND AVAILABLE WITHOUT THE FDA 1–5 (1997) (arguing for removing FDA oversight primarily to eliminate delays in approving new drugs).

³⁴⁶ See Barbara K. Immel, *A Brief History of the GMPs for Pharmaceuticals*, 25 PHARMACEUTICAL TECH. 44, 44–46 (2001). At least part of the problem with relying solely on tort law to govern pharmaceutical manufacturing arises from the difficulty of observing errors, connecting manufacturing errors to injury, and spotting defects that society may wish to prevent but which may not cause cognizable injury—such as overly large fluctuations in the amount of active ingredients. See generally *infra* notes 425–444 and accompanying text (discussing consumers' difficulties of assessing drug quality).

³⁴⁷ See CAMPBELL, *supra* note 345, at 9–16 (discussing the benefits of private third-party regulation).

³⁴⁸ Federal preemption of state drug laws (including tort liability) is a tangled field, with different preemption standards for generics and reference products, drugs, and devices. In addition, different preemption standards apply to enacted state regulation as opposed to requirements imposed by state tort lawsuits. For a summary of this area, see generally Leonard A. Dwarica & Nicholas R. Herrel, *Federal Preemption of Drugs and Devices—Consequences for Injured Patients?*, 25 HEALTH LAW. 4 (2012); Amalea Smirniotopoulos, *Bad Medicine: Prescription Drugs, Preemption, and the Potential for a No-Fault Fix*, 35 N.Y.U. REV. L. & SOC. CHANGE 793 (2011).

³⁴⁹ Telephone Interview with Geoffrey Levitt, Senior Vice President & Assoc. Gen. Counsel, Pfizer (Dec. 20, 2012).

³⁵⁰ See CAMPBELL, *supra* note 345, at 1, 10.

³⁵¹ See *id.* at 9–14 (discussing an example of successful private third-party drug regulation and the possibilities of expanding this model).

would accordingly certify that products were manufactured according to that body's standards.³⁵²

Several concerns arise from such a market certification approach. First, the protection of consumers from dangerous drugs might be considered too important to entrust to private enforcement. Second, the existence of multiple certification bodies could lead to consumer confusion and the potential for a race to the bottom, where different bodies compete in the market to have essentially laxer standards. Because indicators of drug quality are hard for consumers and doctors to evaluate,³⁵³ determining which certification body actually rigorously enforced manufacturing standards and which provided only the patina of respectability might be particularly difficult.³⁵⁴ In addition, certification bodies themselves might steer clear of the market based on liability concerns.³⁵⁵ Furthermore, manufacturing products for sale abroad could encounter major hurdles if only private bodies certified manufacturers.³⁵⁶

More fundamentally, shifting to private certification 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 the FDA and could easily be equally or more risk averse than the FDA.³⁵⁷ In addition,

³⁵² See *id.* This type of mixed private-public regime is employed in other healthcare spheres, including in hospital certification and Institutional Review Boards (“IRBs”). See Timothy Jost, *Health Law and Administrative Law: A Marriage Most Convenient*, 49 ST. LOUIS U. L.J. 1, 9–11 (2004).

³⁵³ See *infra* notes 426–444 and accompanying text (discussing the difficulties of assessing drug quality).

³⁵⁴ IRBs provide a useful comparison. These federally mandated ethics bodies preapprove 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 Studies, Real Harm*, N.Y. TIMES, July 29, 2011, at A27.

³⁵⁵ See CAMPBELL, *supra* note 345, at 15–16.

³⁵⁶ The European Union, for instance, requires that manufacturing controls be certified by a government agency to meet EU standards for any imported medical products. See Directive 2011/62/EU, of the European Parliament and of the Council of 8 June 2011 Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products For Human Use, as Regards the Prevention of the Entry into the Legal Supply Chain of Falsified Medicinal Products, 2011 O.J. (L 174) 74, 78–79, available at http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf, archived at <http://perma.cc/SUH8-DDXS>.

³⁵⁷ Risky actions by the FDA generate backlash, but front-line agents are relatively politically insulated. With a private certification body, the firm and its agents could be subject to private tort liability, leading to increased risk aversion. In contrast, the FDA and its agents are shielded from liability for discretionary decisions by the discretionary function exception to the Federal Tort Claims Act (“FTCA”). 28 U.S.C. § 2680(a) (2012). See generally Donald N. Zillman, *Protecting Discretion: Judicial Interpretation of the Discretionary Function Exception to the Federal Tort Claims Act*, 47

private bodies are just as likely as the FDA to rely on drug characteristics established in clinical trials, as opposed to fundamental science-based specifications. Private oversight, therefore, would likely suffer the same substantive barriers to manufacturing innovation as the current system.

Practically speaking, removing the 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 state or private standards. Private bodies could easily face similar incentives for excessive caution as the FDA. In addition, given diminished consumer perceptions of the pharmaceutical industry, both consumers and the industry may prefer quality oversight by a relatively respected federal government regulator than a private or local body.

2. Mandated Innovation

A second approach involves correcting substantive regulatory hurdles to innovation. The FDA has already taken steps toward this goal in its QbD initiative.³⁵⁸ 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 products; it should be built-in or should be by design."³⁵⁹ More pragmatically, drugs are typically manufactured according to a stable, monitored process designed 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 understandings 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.³⁶⁰ The aim of QbD is that by the time the drugs roll off the production lines, the manufacturer already knows the exact quality of the final products.³⁶¹ End-stage testing is used only to verify quality, not to ensure that the products are high-quality in the first place.³⁶²

ME. L. REV. 365 (1995) (discussing the FTCA and the many cases involving the discretionary function exemption).

³⁵⁸ Anurag S. Rathore & Helen Winkle, *Quality by Design for Biopharmaceuticals*, 27 NATURE BIOTECHNOLOGY 26, 27 (2009). Although QbD-like initiatives exist in other jurisdictions, this Subsection focuses on the regulations and guidance issued by the FDA and the domestic implementation of QbD.

³⁵⁹ *Id.* at 27.

³⁶⁰ Yu, *supra* note 62, at 784.

³⁶¹ *Id.*

³⁶² *Id.*

QbD helps ameliorate substantive obstacles to innovation.³⁶³ If manufacturers have significant knowledge early in the development process—as QbD effectively requires—those drug characteristics that 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 the FDA, substantive calcification may become less necessary. QbD itself is a significant source of manufacturing innovation because it has potential business benefits even without improvements in regulatory oversight.³⁶⁴

The industry is slowly adopting at least parts of QbD, though with major variations across sectors.³⁶⁵ Assessments of QbD adoption differ even within the FDA.³⁶⁶ The FDA has not promulgated regulations enforcing or requiring QbD, but has stated informally that full QbD implementation is expected in the near future.³⁶⁷ 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

³⁶³ See generally *supra* notes 184–204 and accompanying text (discussing substantive FDA barriers to innovation, including regulatory lock-in—which results from manufacturers having to submit their processes for FDA approval before they are able to develop the most efficient methods of production).

³⁶⁴ 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 [a] product will pass specification, giving a more predictable supply chain.” Chris Potter, *PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products*, 4 J. PHARMACEUTICAL INNOVATION 4, 21 (2009). Potential cost savings between \$20 and \$30 billion have been estimated. See Cox, *supra* note 78. Roger Nosal at Pfizer has estimated that QbD saved Pfizer in excess of \$800 million over six or seven years and suggested that similar amounts could apply to other similar companies. Cox, *supra* note 122; see Cox, *supra* note 78.

³⁶⁵ See Joanne Eglovitch, *Generic Industry Has Made Progress Implementing QbD*, GOLD SHEET (Feb. 28, 2013, 12:00 AM), available at <http://www.elsevierbi.com/publications/the-gold-sheet/47/2/generic-industry-has-made-progress-implementing-qbd>.

³⁶⁶ For example, on December 4, 2012, Janet Woodcock, Director of the Center for Drug Evaluation and Research (“CDER”)—a division of the FDA—stated, “I don’t know how widely QbD will be adopted, because there is a significant upfront investment,” and that “I think it’s fair to say, we’re not there yet.” Cox, *supra* note 122. 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,” that “the science and risk-based approaches in QbD [are] being embraced by pretty much all of the innovator pharmaceutical companies,” and finally that “we’re likely past the tipping point in QbD.” *Id.*

³⁶⁷ Nick Taylor, *FDA Developing QbD Examples to Ready Generic Industry for 2013 Deadline*, IN-PHARMA TECHNOLOGIST.COM (Nov. 10, 2011), <http://www.in-pharmatechnologist.com/Processing/FDA-developing-QbD-examples-to-ready-generic-industry-for-2013-deadline>, archived at <http://perma.cc/QK4X-Q9X9> (quoting Lawrence Yu, Deputy Director for Science and Chemistry in the Office of Generic Drugs, as stating that the Office “expects . . . full implementation of QbD in January 2013”).

of January 2013.³⁶⁸ These ANDA submissions, however, appear to prioritize QbD form over substance.³⁶⁹ submissions commonly included a massive amount of information without justification or conclusions, used QbD terminology improperly, or presented prior knowledge without necessary context or justification.³⁷⁰ Thus, the industry still has far to go in actually incorporating QbD methodologies to increase manufacturing efficiency and regulatory efficacy.³⁷¹

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 35 U.S.C. § 271(e)(1) raises enforceability questions for those patents.³⁷² Like other manufacturing techniques, though, QbD techniques are largely protected as trade secrets rather than being patented and thereby publicized.³⁷³

In sum, although QbD involves a regulatory mandate to address at least some of the innovation concerns raised above, it is far from a complete solution. Industry adoption of QbD 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 the FDA. The one incentive associated with QbD, 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.³⁷⁴

³⁶⁸ James, Davidson *FDA Study on the Status of QbD Implementation in the Generic Industry*, LACHMAN CONSULTANTS (Jan. 29, 2013), <http://www.lachmanconsultants.com/fda-study-on-the-status-of-qbd-implementation-in-the-generic-industry.asp>, archived at <http://perma.cc/825R-DE3P>.

³⁶⁹ *Id.*

³⁷⁰ *Id.*

³⁷¹ Cox, *supra* note 122; Ted Fuhr & Katy George, *Moving Beyond the Business Case for QbD*, PHARMA QBD (Mar. 13, 2011), http://www.pharmaqbd.com/mckinsey_beyond_business_case_qbd/, archived at <http://perma.cc/P9Z5-7B6F>. See generally Beth H. Junker, *Building a Business Case for Biopharmaceutical QbD Implementation*, 25 BIOPHARM INT'L 40 (2012) (proposing a model for applying QbD to biopharmaceutical products).

³⁷² See *supra* notes 248–269 and accompanying text (discussing the safe harbor provision of the Hatch-Waxman Act). See generally 35 U.S.C. § 271(e)(1) (2006) (providing that there is no patent infringement if the patented process or technology is only used to prepare submissions to the FDA so that generics may be released as soon as the patent expires).

³⁷³ See Cox, *supra* note 122. 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.” *Id.* He went on to remark that “people are a little reluctant to say how much they’re saving by doing a quality-by-design approach.” *Id.* Similarly, Emil Ciurczak, the President of Doramaxx Consulting, writes, “The reason you don’t hear many hard-core examples is that many companies consider QbD a competitive edge, so [they] don’t want to share—especially with generics.” *Id.* He further notes, “Thus, actual QbD successes are kept under better security than the recipe for Coca-Cola.” *Id.*

³⁷⁴ See *infra* notes 375–388 and accompanying text (explaining that QbD has failed to create regulatory flexibility to spur procedural innovation).

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, as discussed below in Subsection 3.a.³⁷⁵ Regulatory flexibility, however, is an important potential solution on its own merits, as discussed below in Subsection 3.b.³⁷⁶

a. Flexibility and QbD

The 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.³⁷⁷ Process changes within an FDA-approved design space should not require regulatory approval.³⁷⁸ This would allow innovation within a defined set of parameters without regulatory hurdles and would consequently enable more incremental innovation.

Despite at least moderate progress adopting QbD, however, regulatory flexibility has failed to materialize. Instead, FDA reviewers have 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.³⁷⁹ 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.³⁸⁰ Given the significant discretion accorded to such front-line regulators and industry reluctance to challenge exercises of that discretion,³⁸¹ implementing flexibility at the ground level may be particularly challenging.

Policymakers themselves have recognized this failure to achieve regulatory flexibility. Dr. Janet Woodcock, Director of the Center for Drug Evaluation and

³⁷⁵ See *infra* notes 377–383 and accompanying text.

³⁷⁶ See *infra* notes 384–388 and accompanying text.

³⁷⁷ Yu, *supra* note 62, at 788–89. The design space is the multidimensional space which includes all combinations of parameters resulting in the desired final product. See *id.* The acceptable range of parameters varies based on the sensitivity of the process outcome to variation in that parameter. See *id.* 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. See *id.*

³⁷⁸ *Id.* at 789.

³⁷⁹ Eglovitch, *supra* note 40.

³⁸⁰ Telephone Interview with Hedley Rees, *supra* note 332.

³⁸¹ See generally CARPENTER, *supra* note 137, at 635–62 (providing a detailed description of the dynamics between drug manufacturers and the FDA).

Research (“CDER”) at the FDA, recently remarked, “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.”³⁸² FDA Commissioner Margaret Hamburg reiterated this view in February 2013, stating, “[I]n a world where quality risk management is fully embraced, we *could foresee* a time when enhanced regulatory flexibility *might* be possible.”³⁸³ Thus, 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.

b. Flexibility by Voluntary FDA Certification

As an alternative to QbD, regulatory flexibility could come from a new program of voluntary FDA certification of certain manufacturing sites. For sites that consistently demonstrate quality performance above that required by regulation, the FDA could approve increased regulatory flexibility. For example, major changes could be implemented with only notice, rather than preapproval.³⁸⁴ 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.

A system of certified regulatory flexibility would not be entirely novel, but would be new to drug manufacturing. The Occupational Safety and Health Agency (“OSHA”) runs a similar program, wherein worksites that demonstrate safety excellence may seek certification in the Voluntary Protection Programs, subject to renewal every three to five years.³⁸⁵ Although 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.³⁸⁶ The agency, however, still investigates complaints and other significant events.³⁸⁷ Workplaces that participate in OSHA’s program have shown signifi-

³⁸² Cox, *supra* note 122 (citing Janet Woodcock, Dir., Ctr. for Drug Evaluation & Research, Key-note Address at the 2012 IQ Symposium (Dec. 5, 2012)).

³⁸³ Hamburg, *supra* note 112 (emphasis added).

³⁸⁴ See generally *supra* notes 171–183 and accompanying text (discussing the requirements for postapproval filing with the FDA for major, moderate, and minor process changes).

³⁸⁵ See U.S. DEP’T OF LABOR, OCCUPATIONAL SAFETY & HEALTH ADMIN., DIRECTIVE NO. CSP-03-01-003, OSHA INSTRUCTION 8 (2008), available at http://www.osha.gov/OshDoc/Directive_pdf/CSP_03-01-003.pdf, archived at <http://perma.cc/Q28Y-8KRP>.

³⁸⁶ *Id.* at 8–10.

³⁸⁷ *Id.*

cant improvements in worker safety, product quality, and profits.³⁸⁸ A similar program in pharmaceutical manufacturing could offer potentially major benefits without significant regulatory burdens.

4. Altered Regulatory Timelines

Rather than relying solely on procedural or substantive reforms, the 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, INDs in Phase I clinical trials can begin human testing with significantly less stringent requirements for cGMP and Chemistry and Manufacturing Controls ("CMCs") than those required for Phase II or III trials or commercial sale.³⁸⁹ This allows firms to put off developing sophisticated knowledge of a drug's manufacturing characteristics—such as how the drug can best be formulated, what inactive ingredients are most appropriate for final dosage forms, and how fast the drugs should dissolve—until clinical trials have already begun. The actual requirements for CMC and cGMP information when beginning Phase I trials are quite low because the 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 on a commercial scale.³⁹⁰

If the 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, then firms would be forced to generate that additional information before beginning human trials. This would help avoid the current process of locking-in inefficient manufacturing processes and supply chain dynamics.³⁹¹

One downside to this approach is the wasted time and money spent developing information about manufacturability for the vast majority of drugs that will never make it to market. There are two responses that lessen this concern.

³⁸⁸ Brian Bennett & Norman Deitch, *OSHA's VPP: The Value of Participating*, 52 PROF. SAFETY 24, 27, 29 (2007).

³⁸⁹ INDs are still required to comply with § 501(a)(2)(B) of the Food, Drug, and Cosmetic Act, which mandates the use of current good manufacturing practices. See 21 U.S.C. § 351(a)(2)(B) (2012). Under 21 C.F.R. § 210.2(c) (2013), however, 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 Phase III trials or has been marketed. See U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CGMP FOR PHASE I INVESTIGATIONAL DRUGS 1 (2008), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf>, archived at <http://perma.cc/F377-F23K>.

³⁹⁰ Telephone Interview with Hedley Rees, *supra* note 332; see also U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 389, at 12 ("For some materials, all relevant attributes or acceptance criteria may not be known at the phase 1 stage of product development.").

³⁹¹ REES, *supra* note 158, at 405–07.

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—to drugs entering Phase II trials—during which manufacturing information is fully developed and where cGMP regulations come into force. Thus, assuming that the information needs to be generated for drugs in Phase II, and considering that approximately 60% of drugs that enter Phase I trials make it to Phase II trials,³⁹² only 40% of information development costs will be for drugs which ultimately fail—a high fraction, but less than half.³⁹³

Second, and mediating the first response, 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% failed because they were too expensive to manufacture.³⁹⁴ Because later phases of clinical development are significantly more expensive,³⁹⁵ determining earlier that a drug will be too costly to manufacture or too difficult to formulate can reduce costs later in the pipeline. Catching this problem earlier will partially offset the costs of generating unnecessary information for eventually unsuitable candidates.³⁹⁶

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.³⁹⁷

³⁹² Kola & Landis, *supra* note 200, at 713 fig. 1(b).

³⁹³ Approximately 20% of drugs make it from Phase I to Phase III. *Id.*

³⁹⁴ *Id.* at 714 fig. 3.

³⁹⁵ *See id.* at 712.

³⁹⁶ 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. Because 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.

³⁹⁷ *See generally supra* notes 184–204 and accompanying text (discussing the substantive barriers to innovation posed by the FDA's regulations). This approach could also help lessen the problem of mismatches in patent timing described earlier, *see supra* note 247; 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 innovative manufacturer controls the entire market.

5. A Separate Validation Pathway

One final regulatory possibility could address the challenge of FDA reluctance to adopt new technologies by creating a mechanism to validate new technologies detached from the drug approval process. As discussed above, the FDA has historically been reluctant to accept novel technologies, especially in the context of an NDA.³⁹⁸ As a result, because preapproval delay is extremely costly, firms avoid seeking approval in NDAs for novel manufacturing methods.³⁹⁹ This disincentive for manufacturing innovation can be reduced by allowing firms to introduce and validate novel techniques for the FDA separate from any particular NDA.⁴⁰⁰

If firms can demonstrate to the FDA that novel manufacturing techniques function reproducibly and can be validated, then that demonstration could be relied upon by the FDA in any NDA or sNDA seeking to use the new technique. This would be particularly useful for broadly applicable techniques, like HPLC⁴⁰¹ or, more currently, continuous manufacturing dynamically modulated by in-line measurements.⁴⁰² 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.⁴⁰³

A standalone validation process would also ideally be open to firms other than drug sponsors, such as contract manufacturing organizations (“CMOs”), equipment vendors, and manufacturers from other industries. 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,

³⁹⁸ See *supra* notes 142–154 and accompanying text (analyzing the FDA’s preapproval barriers to innovation).

³⁹⁹ See CARPENTER, *supra* note 137, at 67–68. This problem exists principally for preapproval innovation, which would be incorporated into an NDA, because preapproval delay cuts into patent-protected market exclusivity, whereas postapproval delays in implementing manufacturing innovations do not. Restrictions on innovation preapproval, however, also limit the available possibilities for innovation postapproval through the procedural and substantive hurdles previously discussed. See *generally supra* notes 168–204 and accompanying text.

⁴⁰⁰ See DEP’T OF HEALTH & HUMAN SERVS., *supra* note 151, at 147–48 (discussing making “dummy” submissions of new technologies to the FDA—including standard operating procedures—unlinked to any particular NDA to avoid risk of regulatory delay).

⁴⁰¹ See *generally supra* notes 142–154 and accompanying text (discussing the industry’s struggle to obtain FDA approval of HPLC).

⁴⁰² See *generally* Jennifer Markarian, *Process Analytical Technology and Process Control in Solid-Dosage Manufacturing*, 37 PHARMACEUTICAL TECH. 56 (2013) (noting that the industry is moving toward closed-loop control of continuous processing).

⁴⁰³ See CARPENTER, *supra* note 137, at 67–68.

potential clients for a CMO, or patent royalties for any of the above, but especially for 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.

B. Using Regulation to Change Innovation Incentives

Although lowering regulatory barriers could make it easier to innovate, incentives are likely needed to drive optimal innovation past remaining barriers not present in other industries' manufacturing sectors.⁴⁰⁴ 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. The pervasive regulatory oversight in the pharmaceutical industry, and the successful integration of regulation with patent incentives in drug discovery, however, suggest that regulatory structures could 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 accepted. Treating this industry oversight as a given, structural changes with potentially tremendous benefits for innovation could be implemented with relatively small changes and additional costs. Structural improvements could come in two major forms. First, as discussed in Subsection 1 of this Section, 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.⁴⁰⁵ Second, as analyzed in Subsection 2 of this Section, an expansion of regulatory market exclusivity incentives for manufacturing innovation could parallel the

⁴⁰⁴ 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 generally* Fuhr & George, *supra* note 371; Junker, *supra* note 371. Innovation theory, however, 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 *THE RATE AND DIRECTION OF INVENTIVE ACTIVITY* 609, 619, 623 (R.R. Nelson ed., 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 because consumers are relatively cost-insensitive and thus manufacturing costs can be passed on. Quality-increasing innovation may be extremely valuable socially but of relatively low value to manufacturers beyond the quality needed for regulatory approval of market entry because that additional quality, like manufacturing costs, is typically opaque to consumers. *See infra* notes 426–444 and accompanying text (discussing consumers' inability to detect drug quality). Incentives are therefore likely a necessary addition to regulatory improvements to drive socially preferable levels of manufacturing innovation.

⁴⁰⁵ *See infra* notes 407–418 and accompanying text.

existing intellectual property systems, much as regulatory exclusivity for drugs already parallels the patent system.⁴⁰⁶

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, which is driven by the widespread and accurate perception that manufacturing patents are very difficult to enforce successfully.⁴⁰⁷ 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, then firms could more easily rely on them to protect their innovation investments. This swap would trade a typically shorter monopoly period (because trade secrets can exist indefinitely) for easier enforcement upon observation of infringement,⁴⁰⁸ the possibility of greater damages on a finding of willful infringement,⁴⁰⁹ and an environment of easier cumulative innovation, both in-firm and cross-firm.⁴¹⁰ Increasing these incentives and allowing easier cumulative innovation could help increase the efficiency and quality of pharmaceutical manufacturing. In addition, further industry benefits might arise from greater potential mobility of employees unburdened by nondisclosure agreements and consequent knowledge spillovers.⁴¹¹ Benefits to those outside the industry would include increased disclosure of whatever manufacturing innovations are generat-

⁴⁰⁶ See *infra* notes 419–425 and accompanying text.

⁴⁰⁷ See *supra* notes 223–269 and accompanying text (discussing patents in the pharmaceutical industry).

⁴⁰⁸ Proving misappropriation of trade secrets in court is very challenging, including proving that secrets were adequately protected and that misappropriation occurred instead of independent invention. See Gene Rzucidlo & Stefan Miller, *Aggressive Intellectual Property Strategies*, in BEST PRACTICES IN BIOTECHNOLOGY BUSINESS DEVELOPMENT: VALUATION, LICENSING, CASH FLOW, PHARMACOECONOMICS, MARKET SELECTION, COMMUNICATION, AND INTELLECTUAL PROPERTY, *supra* note 286, at 61, 65.

⁴⁰⁹ See 35 U.S.C. § 284 (2006 & Supp. V 2011) (providing that the court may award damages “adequate to compensate for the infringement”).

⁴¹⁰ See generally Erkal, *supra* note 327 (examining the best trade secret policies for encouraging cumulative innovation); Scotchmer, *supra* note 31 (discussing the importance of continual improvements on initial innovations); *supra* notes 326–331 and accompanying text (discussing structural disadvantages of a trade secret regime).

⁴¹¹ See generally Matt Marx et al., *Regional Disadvantage? Non-Compete Agreements and Brain Drain* (Nat'l Sci. Found., Working Paper, 2010), available at <http://papers.ssrn.com/abstract=1654719>, archived at <http://perma.cc/WFZ2-GDRU> (arguing that noncompete agreements for employees prevent inventor mobility and cause good inventors to leave states that do enforce these agreements for states that do not).

ed, the possibility of greater manufacturing transparency, and the societal benefits of increased cumulative innovation.⁴¹²

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 transparent so that patent infringement could be detected and the patent subsequently enforced.⁴¹³ 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 the FDA of the details of their manufacturing procedures and are subject to FDA inspections. Although actually *enforcing* manufacturing patents is well outside the scope of the FDA's authority, making publically available the registered manufacturing techniques and other manufacturing information currently maintained confidentially by the FDA would allow firms to police their patented techniques themselves. Such an approach would not be easy. In particular, there are significant statutory and potential constitutional problems with revealing information previously disclosed to the FDA confidentially.⁴¹⁴ As a prospective solution for NDAs, AN-DAs, and other manufacturing changes going forward, however, this idea faces fewer challenges.

⁴¹² 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, because independent invention is a defense against trade secret misappropriation actions but not patent infringement actions. DEAN RUSSELL ET AL., CHOOSING BETWEEN TRADE SECRET AND PATENT PROTECTION 18, available at <https://clients.kilpatricktownsend.com/IPDeskReference/Documents/Trade%20Secret%20or%20Patent%20Protection.pdf>, archived at <http://perma.cc/VE3N-XAZC>.

⁴¹³ If injunctive enforcement blocking cumulative innovation were a major worry, a mandatory licensing regime could be contemplated instead. *Cf.* *eBay v. MercExchange*, 547 U.S. 388, 393–94 (2006) (holding that permanent injunctive relief should issue in patent infringement cases only after a showing of the four traditional equitable factors and reversing the Federal Circuit's general rule favoring permanent injunctions).

⁴¹⁴ 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, 291–99 (2011). On the other hand, in 1974, in *Kewanee Oil v. Bicron Corp.*, the U.S. Supreme Court held that state trade secrecy regimes were not preempted by the federal patent system, but also noted:

If a State, through a system of protection, were to cause a substantial risk that holders of patentable inventions would not seek patents, but rather would rely on the state protection, we would be compelled to hold that such a system could not constitutionally continue to exist. In the case of trade secret law no reasonable risk of deterrence from patent application by those who can reasonably expect to be granted patents exists. Trade secret law provides far weaker protection in many respects than the patent law.

416 U.S. 470, 489–90 (1974). A colorable argument could be made, though it is outside the scope of this Article, that drug manufacturing processes—or even manufacturing processes in general—face weak enough protection under patent law that the availability of state trade secret protection actually deters innovators from seeking patent protection. If that were indeed the case, trade secret protection for those innovations might be constitutionally suspect, and mandatory disclosure of those innovations might not be a taking requiring compensation. *Cf. id.*

In fact, Congress has already mandated a limited version of this approach in the approval process for biosimilars as authorized by the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”).⁴¹⁵ The BPCIA created an abbreviated approval pathway for biosimilars, but within twenty days of the FDA’s acceptance of an application for a biosimilar, the applicant must provide a copy of the application to the reference product sponsor, including the method by which the biosimilar is manufactured.⁴¹⁶ 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.⁴¹⁷ 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.⁴¹⁸ 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 the industry. Nevertheless, manufacturers require more complex new technologies to manage and evaluate production, especially for biologics. Thus, broad and cumulative innovation could well be worth the costs of mandated transparency.

2. A Parallel Regulatory Exclusivity Regime for Manufacturing Innovation

Rather than trying to shift the industry from a trade secrecy regime to a patent-based regime for manufacturing innovation, the FDA could administer a parallel set of market protection incentives that could be more carefully tailored to industry dynamics than patent or trade secrecy regimes. Currently, FDA market protection is statutorily available only for innovations in drug discovery or development. The market protection 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 innovative manufacturing process or to a related or unrelated drug.

To address the less intuitive but more familiar solution first, the 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

⁴¹⁵ Pub. L. No. 111-148, 124 Stat. 804 (2010) (codified at 42 U.S.C.A. § 262 (West 2011 & Supp. 2013)).

⁴¹⁶ 42 U.S.C. § 262(l)(2)(A).

⁴¹⁷ *Id.* § 262(l)(1)(B)–(D). Unlike small-molecule drugs, for which patents are centrally registered in the Orange Book, patents on biologics are not registered. Dougherty, *supra* note 242, at 234. The BPCIA thus sets up a complex scheme in which the pioneer and follow-on manufacturers exchange information on relevant patents. *Id.*; see § 262(l).

⁴¹⁸ 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.

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, the 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.⁴¹⁹ Such a linked approach would be harder to apply to manufacturing innovations that 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.⁴²⁰ Such wild-card extensions have been previously suggested as regulatory prizes for different types of pharmaceutical innovation.⁴²¹

There are significant concerns with product-based regulatory exclusivity, centered on appropriately valuing the innovation. For example, the FDA might have difficulty determining whether a manufacturing innovation is significant enough to merit the bonus of regulatory exclusivity. In addition, the FDA would need some mechanism of screening out useful innovations from marginal or inefficient innovations to avoid a situation where small manufacturing changes continually extend drug exclusivity. 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.⁴²² 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 before implementation. Thus, if a company demonstrated an innovative and useful major change in manufacturing, and the FDA approved it for that company, then the FDA could register the change and explicitly refuse to approve other compa-

⁴¹⁹ See 21 U.S.C. § 355a(b) (2012); *supra* note 274 and accompanying text.

⁴²⁰ See Amy Kapczynski, *Commentary: Innovation Policy for a New Era*, 37 J.L. MED. & ETHICS 264, 265–66 (2009).

⁴²¹ See *id.*

⁴²² 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 that would overlap with the period of regulatory exclusivity would receive less benefit from the exclusivity than firms without patent protection.

nies' implementations of that change for a period of time.⁴²³ Once the exclusivity period expired, all pending manufacturing change applications to use the innovative process could be automatically 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 the 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 the FDA to then prevent other manufacturers from using the same procedure. In other contexts, however, the FDA similarly prioritizes innovation incentives. For instance, pediatric studies are rewarded with exclusivity for the entire drug line, for all uses, not just pediatric uses.⁴²⁴ This drug-line exclusivity sacrifices access to a drug for the sake of more information for pediatric users.⁴²⁵ 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. Because the FDA oversees pharmaceutical manufacturing, requires registration of manufacturing techniques, and preapproves 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, then firms might avoid seeking that exclusivity to avoid that disclosure. Avoiding disclosure is a key reason why patents are already ineffective. But, if FDA exclusivity occurs without public disclosure, then the social and industrial benefits of such 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 indica-

⁴²³ It is an arguable question, although outside the scope of this Article, whether the 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.

⁴²⁴ See 21 U.S.C. § 355a(b); *Nat'l Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 38–41 (D.D.C. 1999).

⁴²⁵ See *Henney*, 47 F. Supp. at 38–41.

tion. It would demand that the agency make hard judgments about which 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. The FDA currently lacks the institutional competence—and the mandate—to develop a truly parallel pseudo-patent system alongside the actual patent regime.

Overall, although 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, and it has been previously applied 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. Nevertheless, because the drug market is effectively unable to recognize or reward manufacturing quality, the market does not demand a particular quality of product.⁴²⁶ Janet Woodcock recently noted this in the context of drug shortages, specifically shortages of generic sterile injectables.⁴²⁷ A key reason for those shortages is that healthcare consumers (whether doctors, hospitals, or the group purchasing organizations that act as middlemen in many drug markets) are unable to discern differences in quality between the products of different manufacturers.⁴²⁸ Because all generic versions of a drug 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.”⁴²⁹

⁴²⁶ Woodcock & Wosinska, *supra* note 72, at 171–72.

⁴²⁷ *Id.* at 171.

⁴²⁸ *Id.*

⁴²⁹ *Id.* In addition, in the specific markets analyzed, quality may be especially difficult to measure after the fact. In many markets, even if there is no ex ante way for consumers to differentiate products based on quality, products can be differentiated ex post based on product performance and the rate of product failure. Sterile injectable and infusible drugs, however, are usually administered to patients who have compromised immune systems and lack the ability to effectively fight infections. *Id.* at 172. Accordingly, drug contamination events are difficult to differentiate from infections that 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

Accordingly, manufacturers compete only on price, not on quality, resulting in nonrobust manufacturing procedures prone to breakdowns and causing shortages.⁴³⁰

This lack of quality competition is hard for consumers, insurers, and the FDA itself to detect. Microbial contamination, in particular, can be episodic and non-uniform;⁴³¹ a poorly maintained or designed production line may only intermittently introduce contamination, which may itself be relatively benign or very harmful.⁴³² Thus, traditional after-the-fact sampling protocols performed by the manufacturer and reviewed by the FDA may miss sources of contamination.⁴³³ Contributing to the lack of regulatory incentives for maintaining the highest quality standards, the FDA's response to contamination events is frequently tempered by its desire to avoid drug shortages.⁴³⁴ Thus, manufacturers face both a market that is approximately indifferent to quality—because quality is hard to observe—and one that has a regulatory structure that can only occasionally detect quality problems and that imposes a restrained response.⁴³⁵

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.”⁴³⁶ Many manufacturers therefore “minimize quality system investments.”⁴³⁷

To cope with the lack of quality awareness, particularly in the market, Dr. Woodcock suggests that “[the] FDA could support buyers and payers in their purchase and reimbursement decisions by providing them with meaningful manufacturing quality metrics.”⁴³⁸ Such metrics would be analogous to the use of

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.* As a result, few providers will make the causal link and report that an adverse event is based on manufacturing problems. *Id.*

⁴³⁰ *Id.*

⁴³¹ *Id.*

⁴³² *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.

⁴³³ *Id.* at 172.

⁴³⁴ *Id.*

⁴³⁵ *Id.*

⁴³⁶ *Id.*

⁴³⁷ *Id.* at 175. Woodcock did note though that “many 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 straight 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.

⁴³⁸ *Id.* at 175.

scorecards for Health Management Organizations (“HMOs”)⁴³⁹ or grades given to restaurants by health inspectors.⁴⁴⁰ They would demonstrate quality above that required by cGMP regulations.⁴⁴¹ The FDA is currently planning to create a drug quality program implemented by a newly instituted Office of Pharmaceutical Quality within CDER.⁴⁴²

Although 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. Institutional purchasers (who dominate the market for many drugs with the most prevalent manufacturing quality issues), however, may not be concerned about minor differences in quality as long as the firm has met the FDA’s marketability threshold. Because FDA certification provides a basic quality guarantee, liability would be unlikely to result from failing to pay a premium for additional manufacturing quality.⁴⁴³ 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. Institutions could therefore 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 the 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

⁴³⁹ *Id.* In California, the state provides quality ratings for health insurance plans, including HMOs, as well as for health care providers. *California Health Care Quality Report Cards*, STATE CAL., <http://www.opa.ca.gov/Pages/ReportCard.aspx>, archived at <http://perma.cc/3RQA-HZ8M> (last visited Feb. 14, 2014).

⁴⁴⁰ See *Restaurant Inspection Results (Letter Grades)*, N.Y. CITY DEPARTMENT HEALTH & MENTAL HYGIENE, <http://www.nyc.gov/html/doh/html/services/restaurant-inspection.shtml>, archived at <http://perma.cc/87LH-3QLW> (last visited Feb. 14, 2014).

⁴⁴¹ Technically, under FDA cGMP standards, any adulteration of a drug subjects the manufacturer 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 $\pm 10\%$ range typically permitted by the FDA, continuous process monitoring, or very high ingredient purity.

⁴⁴² Hamburg, *supra* note 112.

⁴⁴³ As noted before, tort preemption is a particularly tangled doctrine at the moment and may change. See *supra* note 348.

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.⁴⁴⁴ 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. And generic companies, to avoid exclusion from the market, would need to 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 arising from decreased or delayed generic entry.

CONCLUSION

This Article has argued that studies of innovation policy in the pharmaceutical industry at the policy level and in academia 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 several barriers to manufacturing innovation and an intellectual property regime poorly aligned to incentivize 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 in manufacturing processes, particularly in the pharmaceutical industry. New products must be made and distributed for society to receive their benefit. Although society assumes that manufacturing and distribution are straightforward, the case of the pharmaceutical industry demonstrates that this assumption is not always true. Profoundly problematic consequences arise when regulations and incentives actively hinder manufacturing innovation. 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 legal rules significantly slow innovation.

This policy gap regarding different forms of innovation, however, 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, and manufacturing those drugs is another area for regulation to press forward. A parallel system of intellectual property incentives, or more drastic changes that shift the way already existing incentives function in the in-

⁴⁴⁴ C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. EMPIRICAL LEGAL STUD. 613, 632–33 (2011).

dustry, are two major possibilities. Other options may also 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, 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.