Manufacturing Barriers to Biologics Competition and Innovation

W. Nicholson Price II[*] *& Arti K. Rai*[**]

ABSTRACT: As finding breakthrough small-molecule drugs becomes more difficult, drug companies are increasingly turning to "large molecule" biologics. Although biologics represent many of the most promising new therapies for previously intractable diseases, they are extremely expensive. Moreover, the pathway for generic-type competition set up by Congress in 2010 is unlikely to yield significant cost savings.

This Article provides a fresh diagnosis of and prescription for this major public policy problem. It argues that the key cause is pervasive trade secrecy in the complex area of biologics manufacturing. Under the current regime, this trade secrecy, combined with certain features of Food and Drug Administration ("FDA") regulation, not only creates high barriers to entry of indefinite duration but also undermines efforts to advance fundamental knowledge about how biologics function and are best produced.

In sharp contrast, offering incentives for information disclosure to originator manufacturers would leverage the existing interaction of trade secrecy and the regulatory state in a positive direction. Trade secrecy, particularly in complex areas like biologics manufacturing, often involves tacit knowledge that is difficult to codify and thus transfer. In this case, however, regulatory requirements mandate that originator manufacturers submit manufacturing details. As a consequence, manufacturers have already codified the relevant tacit knowledge. Carefully structured mechanisms for incentivizing disclosure of these regulatory submissions would not only spur competition, but would

---

* Assistant Professor of Law, University of New Hampshire School of Law; Ph.D. Biological Sciences, Columbia University, 2010.

** Elvin R. Latty Professor of Law, Duke Law School; Faculty Co-Director, Duke Law Center for Innovation Policy.

Thanks to Jamie Boyle, Molly Van Houweling, Peter Menell, Barak Richman, Jacob Sherkow, Michael Tarlov, Jonathan Wiener, and Gillian Woollett for helpful discussions and comments. We presented earlier versions of this Article at Boalt Law School, Duke Law School, the 2014 Intellectual Property Scholars Conference, and the 2015 Works-In-Progress in Intellectual Property ("WIPIP") Colloquium. We thank the participants in those fora for their questions and comments. Rai's research on this Article was supported by NIH's National Human Genome Research Institute under Grant P50 HG003391. Any errors are, of course, our own.

also provide a rich source of information upon which additional research, including fundamental research into the science of manufacturing, could build.

In addition to providing a fresh diagnosis and prescription in the specific area of biologics, this Article contributes to more general scholarship on trade secrecy and tacit knowledge. Prior scholarship has neglected the extent to which regulation can turn tacit knowledge not only into codified knowledge but into precisely the type of codified knowledge that is most likely to be useful and accurate. This Article also draws a link to the literature on adaptive regulation, arguing that greater regulatory flexibility is necessary and that more fundamental knowledge should spur flexibility.

I. INTRODUCTION

Most drugs are small. Aspirin, for instance, is made up of just 21 atoms. Small drugs like aspirin provide the majority of global revenue for brand-name drug companies. But finding new small-molecule drugs keeps getting harder, and generic drug manufacturers are quick to compete with brand-name firms once patents expire.[1] As a result, drug companies are increasingly turning to very large drugs: biologics produced by living cells.[2] In terms of size and rough complexity, if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet.[3] Biologics provide promising new avenues for doctors to better treat patients, and—not coincidentally—for drug companies to profit. But making biologics is more complex than making small-molecule drugs, and that complexity raises serious challenges for innovation and competition policy in the biopharmaceutical industry.

Biologics represent attractive investment opportunities for drug companies. Spending on small-molecule drugs is close to stagnant, especially in developed countries. In contrast, annual global spending on biologics was $93 billion in 2006, rose 69% to $157 billion in 2011, and is expected to rise another 30%, to between $200 billion and $210 billion in 2016.[4]

In the United States, percentage expenditures on biologics will be even more substantial. Indeed, some health care industry analysts predict that in the United States so-called specialty drugs—a category that overlaps substantially with biologics—will represent half of annual prescription drug spending by 2020.[5]

To some extent, the money reflects changes in medicine: Biologics represent many of the most prominent, and promising, new treatments for cancer and other major diseases. They include Avastin, an anti-cancer therapeutic protein with $6.1 billion in global 2012 sales; and the three best-selling therapies of 2012, Humira ($9.3 billion), Remicade ($9.1 billion), and Enbrel ($8.1 billion), each used to treat rheumatoid arthritis.[6]

---

1. *See, e.g.*, Arti K. Rai et al., *Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery*, 8 YALE J. HEALTH POL'Y L. & ETHICS 1 (2008).

2. *See infra* notes 29–34.

3. Deepak Gupta et al., *A CMO Perspective on Quality Challenges for Biopharmaceuticals*, BIOPROCESS INT'L (Oct. 1, 2013, 9:00 AM), http://www.bioprocessintl.com/manufacturing/antibody-non-antibody/a-cmo-perspective-on-quality-challenges-for-biopharmaceuticals-347335.

4. IMS INST. FOR HEALTHCARE INFORMATICS, THE GLOBAL USE OF MEDICINES: OUTLOOK THROUGH 2016, at 9 (2012), https://www.imshealth.com/files/web/IMSH%20Institute/Reports/The%20Global%20Use%20of%20Medicines%20Outlook%20Through%202016/Medicines_Outlook_Through_2016_Report.pdf. In 2016, the global market for small-molecule drugs and biologics will be $1.2 trillion. *Id.* at 5. The global percentage share for biologics in 2016 will be about 16%. *Id.* at 4.

5. SUZANNE M. KIRCHHOFF, CONG. RESEARCH SERV., R44132 SPECIALTY DRUGS: BACKGROUND AND POLICY CONCERNS 2 (2015).

6. *Biologic Drugs Set to Top 2012 Sales*, 18 NATURE MED. 636, 636 (2012).

But total sales revenues also reflect high prices. Although biologics are prescribed less frequently than the most popular small-molecule drugs, they have an average daily cost in the United States that is 22 times higher than small-molecule drug therapies.[7]

Differences in intellectual property protection drive much of the price differential between small molecules and biologics. In general, under the Hatch–Waxman Act of 1984, the originator firms' small molecules are protected by patents and by a short (five-year) period of exclusivity over the clinical trial data the originator must generate to secure approval by the Food and Drug Administration ("FDA"). After that short exclusivity period, Hatch–Waxman treats the originator clinical trial data as informational infrastructure whose social value is maximized through some level of competitor access.[8] Specifically, competitors can bypass conducting their own duplicative clinical trials on the same molecule and secure FDA approval based on the originator firm's data. The five-year regulatory exclusivity, which begins once originator marketing has begun, typically expires well before originator patents expire. Thus, once small-molecule patents expire, the usual result is pricing at or near marginal cost. Generics now represent more than 80% of all small-molecule prescriptions in the United States.

In contrast, until 2010—more than three decades into the biotechnology revolution and well after many relevant patents had begun to expire—the United States had no mechanism by which competitors could rely on originator data for biologics. And only as of July 2014, four years after the establishment of a "follow-on" pathway in the 2010 Biologics Price Competition and Innovation Act ("BPCIA"),[9] did the FDA finally accept its first application for a "follow-on" biologic.[10] In contrast, the European

7. Elizabeth Richardson, *Biosimilars: To Encourage Competition, the Health Care Law Directs the FDA to Develop an Accelerated Approval Pathway for Follow-on Versions of Original Biologic Products*, HEALTH AFF.: HEALTH POL'Y BRIEF (Oct. 10, 2013), http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_100.pdf.

8. *See generally* BRETT M. FRISCHMANN, INFRASTRUCTURE: THE SOCIAL VALUE OF SHARED RESOURCES (2012) (discussing a broad range of contexts where a resource's social value can be maximized through some level of shared access).

9. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111–148, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (codified as amended at 42 U.S.C. § 262 (2012)). The BPCIA was passed as part of the Patent Protection and Affordable Care Act ("ACA").

10. In January 2015, an FDA scientific advisory board undertook the next step and recommended that the FDA approve the biosimilar application for filgrastim. *Sandoz Biosimilar Filgrastim Recommended for Approval by FDA Oncologic Drugs Advisory Committee*, SANDOZ, http://www.sandoz.com/media_center/press_releases_news/global_news/2014_01_07_Sandoz_biosimilar_filgrastim_recommended_for_approval_by_FDA_Oncologic_Drugs_Advisory_Committee.shtml (last visited Jan. 10, 2015). The FDA officially approved the application on March 6, 2015. Press Release, U.S. Food & Drug Admin., FDA Approves First Biosimilar Product Zarxio (Mar. 6, 2015), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm. The brand-name, or reference, product for filgrastim is Amgen's Neupogen. *Id.* Perhaps not surprisingly, on the spectrum of biologics complexity, filgrastim is relatively simple, weighing in at 18,880 Daltons. *See* Anurag S. Rathore & Rahul Bhambure, *Establishing Analytical Comparability*

Medicines Agency ("EMA") started approving follow-on biologics in 2006 and has now approved 21 follow-on, or biosimilar, products.[11]

Commentators have discussed the very substantial lag in U.S. development of a follow-on pathway.[12] They have also discussed distortions in research and development portfolios that might be caused by the congressional decision to confer upon originator biologics firms a 12-year period of data exclusivity while retaining the five-year period for small molecules.[13] Much less discussed, but perhaps more profound in the long term, is the significant barrier to biologic-market entry that may persist indefinitely as a consequence of the trade secrecy pervasive in the field of biologics manufacturing.

This trade secrecy is critical because, unlike small molecules, many complex biologic products cannot be fully characterized by current techniques for analyzing the end product.[14] Moreover, slight variations in the manufacturing process can change the quality, safety, or efficacy of the final product. Thus while generic entrants in the area of small molecules can readily characterize the brand-name product and then reverse engineer one or more chemical synthetic paths to the product, biosimilar competitors face a much more strenuous and expensive task.

European biosimilar product manufacturers have on average expended between $100 million and $250 million and seven to eight years in the reverse engineering necessary to bring these products to market.[15] This cost is likely to rise as biologics that are particularly difficult to manufacture, such as monoclonal antibodies, begin to dominate the market.[16] In comparison, the cost of bringing a generic small-molecule to market may be as low as $1 million to $2 million.[17]

Perhaps not surprisingly, then, European countries have seen only modest price reductions for biosimilars. The average price discount is about 25%, and by 2020 the *total* cost savings from biosimilar introduction in

---

for "Biosimilars": Filgrastim As a Case Study, 406 ANALYTICAL & BIOANALYTICAL CHEMISTRY 6569, 6574 fig.4 (2014).

11. *See Biosimilars Approved in Europe*, GENERICS & BIOSIMILARS INITIATIVE ONLINE (Feb. 27, 2015), http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe.

12. *See, e.g.*, Benjamin P. Falit et al., *Biosimilar Competition in the United States: Statutory Incentives, Payers, and Pharmacy Benefit Managers*, 34 HEALTH AFF. 294, 295 (2015).

13. *See* Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 547–55 (2011). In contrast, the European Union has the same period of regulatory exclusivity for both small molecules and drugs. *See id.*

14. *See infra* Part II.B.

15. Gary Walsh, *Biopharmaceutical Benchmarks 2014*, 32 NATURE BIOTECHNOLOGY 992, 995 (2014).

16. *See generally id.*

17. OFF. OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION, U.S. DEP'T OF HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS 4–5 (2010), http://aspe.hhs.gov/basic-report/expanding-use-generic-drugs.

Europe will likely range from $15 billion to $44 billion.[18] Analysts have projected similarly modest, or even lower, cost savings in the United States over the next decade.[19] In contrast, although the generic entry regime for small molecules set up by the Hatch–Waxman Act of 1984 does allow some gaming of the regulatory system (and much scholarly ink has been spilled on such gaming),[20] reputable estimates suggest that generic entry under Hatch–Waxman has saved U.S. consumers as much as *$1 trillion* between 1999 and 2010.[21]

Addressing the trade secret challenge is far from obvious. Indeed, most commentators who have noted the issue appear to have accepted the biosimilar path's limitations, perhaps with the hope that the cost of reverse engineering by follow-on manufacturers will eventually diminish as analytic techniques slowly improve, relationships between process and product slowly become better understood, and at least some of this knowledge becomes accessible to biosimilar manufacturers.[22] Given the very substantial cost challenge posed by biologics, a more proactive approach seems appropriate.

The proactive approach that some countries use—government-imposed price regulation of originator products—misses the mark. Putting aside

18. Francis Megerlin et al., *Biosimilars and the European Experience: Implications for the United States*, 32 HEALTH AFF. 1803, 1805–06 (2013).

19. Henry G. Grabowski et al., *Regulatory and Cost Barriers Are Likely to Limit Biosimilar Development and Expected Savings in the Near Future*, 33 HEALTH AFF. 1048, 1056 (2014) (arguing that "the relatively moderate estimate by the Congressional Budget Office (CBO) of a cumulative $25 billion in total cost savings from the use of biosimilars over the first decade after the [BPCIA's] passage . . . looks overly optimistic").

20. According to critics of the practice, branded firms game the system by seeking secondary patents of dubious validity and then paying generic entrants not to challenge the patents. *See, e.g.*, Daniel A. Crane, *Per Se Illegality for Reverse Payment Patent Settlements?*, 61 ALA. L. REV. 575, 577 (2010); Gregory Dolin, *Reverse Settlements as Patent Invalidity Signals*, 24 HARV. J.L. & TECH. 281, 283 (2011); C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch–Waxman Act*, 77 ANTITRUST L.J. 947, 948 (2011). The Supreme Court's 2013 decision in *Federal Trade Commission v. Actavis, Inc.*, 133 S. Ct. 2223, 2227 (2013), applies antitrust law to place constraints on these so-called reverse payments. But even the Federal Trade Commission, a major executive branch critic of reverse payments, estimates that an outright ban on such payments would save consumers a relatively modest $35 billion over the next decade. *See* Jon Leibowitz, Chairman, Fed. Trade Comm'n, "Pay-for-Delay" Settlements in the Pharmaceutical Industry: How Congress Can Stop Anticompetitive Conduct, Protect Consumers' Wallets, and Help Pay for Health Care Reform (The $35 Billion Solution) (June 23, 2009), https://www.ftc.gov/sites/default/files/documents/public_statements/pay-delay-settlements-pharmaceutical-industry-how-congress-can-stop-anticompetitive-conduct-protect/090623payfordelayspeech.pdf.

21. GENERIC PHARM. ASS'N, GENERIC DRUG SAVINGS IN THE U.S. 3 (4th annual ed. 2012), http://www.ahipcoverage.com/wp-content/uploads/2012/08/2012-GPHA-IMS-GENERIC-SAVINGS-STUDY.pdf. Although some have criticized these IMS studies for failing to account for confidential discounts brand-name manufacturers have given purchasers, recent IMS Health estimates of these discounts suggest that they only would reduce the $1 trillion figure by about 20%. *See* IMS INST. FOR HEALTHCARE INFORMATICS, *supra* note 4, at 3.

22. *See, e.g.*, Grabowski et al., *supra* note 19.

political feasibility,[23] such price regulation mistakenly views the problem as one of natural monopoly.[24] The problem is instead one of information sharing, and price regulation does nothing to foster the disclosure necessary to foster information-based innovation.

Because the problem is one of information sharing, price regulation also fails to address the suboptimal incentive for originator manufacturers to disseminate, and likely even to generate, fundamental knowledge about biologics manufacturing processes. As we will discuss, this suboptimal incentive emerges not only from well-understood economic principles governing basic research, but also from the nature of post-approval federal regulatory oversight over manufacturing process details.

This Article undertakes what is to our knowledge the first comprehensive scholarly inquiry into the problem of secret biologics manufacturing processes.[25] This Article argues that policy interventions encouraging greater information disclosure and generation, both by individual originator firms and through public–private consortia, would yield both cost efficiencies and innovation gains.[26]

With respect to individual firms, one option might involve greater disclosure of manufacturing processes in the product/composition-of-matter patent applications brand-name manufacturers file. Although existing patent law requires substantially more disclosure than biopharmaceutical applicants provide, simply requiring more disclosure would likely lead originator firms to abandon the patent path altogether. In this context, trade secrecy appears

---

23. Notably, the politically controversial ACA, which expands insurance coverage and regulates most insurance plans, does not attempt any type of price regulation of biologics. Instead, it "caps patients' total out-of-pocket spending [insurance companies can impose] at approximately $6,500 for individuals and $13,000 for families." *See* Falit et al., *supra* note 12, at 299. These caps may actually create another shelter from competition for originator biologics firms. Some have argued that even if biosimilars do come on the market at somewhat reduced prices, these caps make insured patients less price-sensitive and thus less likely voluntarily to choose biosimilars. *Id.*

24. *See generally* William J. Baumol, *On the Proper Cost Tests for Natural Monopoly in a Multiproduct Industry*, 67 AM. ECON. REV. 809 (1977) (attempting to correct ambiguity in the term "natural monopoly").

25. To the extent commentators have engaged the issue, they have generally argued that patents covering biologics may be invalid because they do not disclose how to make the biologic. *See, e.g.*, Dmitry Karshtedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109 (2011); Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH., Fall 2006, at 1. However, as we note below and discuss at length in Part IV, mandating more disclosure in patents is unlikely to generate disclosure of the trade secrets that are most relevant.

26. We focus here on trade secrecy in the federal regulatory state and thus do not address whether changes to state law that would discourage covenants not to compete and other restrictions on employee mobility might promote socially beneficial diffusion of relevant information across firms. *See generally* ORLY LOBEL, TALENT WANTS TO BE FREE: WHY WE SHOULD LEARN TO LOVE LEAKS, RAIDS, AND FREE RIDING (2013).

more privately valuable than patents. And invalidation of patents already granted on grounds of inadequate disclosure is not going to spur greater disclosure.

Our preferred approach capitalizes on the existing interaction of trade secrecy with the regulatory state. As this Article will discuss, the interaction currently reinforces barriers to biologic market entry, but it could be leveraged in a more positive direction.

Specifically, although trade secrecy often involves tacit knowledge that is difficult to transfer, the FDA regulatory requirements mandating that originator manufacturers submit manufacturing details has already turned tacit knowledge into codified information. This codified information is already subject to the usual economics associated with codification: low marginal cost of transfer and replication.[27] Moreover, originators' interest in getting their biologic approved ensures that this codified knowledge is presented in a manner that is useful and accurate.

Additionally, because FDA approval represents the time by which relevant manufacturing process information must be fully developed and codified, disclosure tied to FDA approval is superior to disclosure within the patent system. Indeed, tying information disclosure to FDA approval has some existing precedent. As discussed in Part IV, the BPCIA already requires some level of manufacturing process disclosure on the part of the biosimilar manufacturer.

Although disclosure could in theory be elicited either through incentives or mandates, incentives are likely superior. Even putting aside political feasibility, mandates may unduly undermine incentives, and in any event the takings doctrine likely limits the ability to use mandates that have retroactive impact.

Disclosure linked to FDA regulatory levers would be valuable not only for competition but also for innovation. In particular, it would provide a rich source of information upon which fundamental research into the science of manufacturing could build. But independent of whether such disclosure comes to pass, more fundamental research is essential. Nascent initiatives by the National Institute of Standards and Technology ("NIST") to use public–private consortia to generate such fundamental knowledge and place it in the public domain are likely to yield substantial benefits for both competition and innovation.

As noted, we believe this Article's analysis represents the first comprehensive examination of the major public policy challenge posed by trade secrecy in biologics manufacturing. Of course, the question of trade secrecy in processes, or in the regulatory State, is not new. This Article draws

27. *See, e.g.*, 1 DAVID J. TEECE, ECONOMIC PERFORMANCE AND THE THEORY OF THE FIRM: THE SELECTED PAPERS OF DAVID J. TEECE 398–99 (1998) (comparing low costs of technology transfer involving codified knowledge with high costs involving tacit knowledge).

upon, and contributes to, a number of active scholarly debates on such trade secrecy. In terms of contribution, prior literature on trade secrecy in the regulatory State has not emphasized the extent to which regulation can turn tacit industry knowledge not only into codified knowledge but into precisely the codified knowledge that is most likely to be useful and accurate. This Article also draws a heretofore underexplored link to the literature on adaptive regulation, arguing that greater regulatory flexibility on the part of the FDA is necessary and that more fundamental knowledge about biologics manufacturing processes should spur flexibility.

Part II of this Article presents the basic scientific and regulatory framework. Part III highlights the large efficiency distortions created by the framework.[28] Part IV presents policy prescriptions. Part V discusses the link to the literature on adaptive regulation.

II. BIOLOGIC MANUFACTURING AND BIOSIMILARS

Biologics are complex macromolecular therapeutics produced by living sources rather than through chemical synthesis.[29] Biologics as a class include therapeutic proteins, toxins and antitoxins, viruses, blood and blood products, gene therapy products, and whole cells, among others.[30] As a general matter, they are much more complex than traditional small-molecule drugs.[31] Therapeutic protein biologics—the class of biologics on which we

28. Of course, in the health context, many would argue that values other than efficiency are quite important. For present purposes, this Article need not squarely engage this important debate, as the efficiency-related objectives of reducing deadweight loss and duplicative research point in the same direction as distributive justice and prevention of harm to human subjects through duplicative clinical trials.

29. Jordan Paradise, Foreword, *Follow-on Biologics: Implementation Challenges and Opportunities*, 41 SETON HALL L. REV. 501, 502–03 (2011).

30. Section § 262(i) of the BPCIA defines biologics as

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. § 262(i) (2012). FDA guidance under the BPCIA specifies that any intervention greater than 40 amino acids is considered a biologic "protein" unless it is made entirely through chemical synthesis and is under 100 amino acids. FOOD & DRUG ADMIN. ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY 24 (2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

31. However, because a few biologics are relatively simple, the BPCIA definition provided some clarity. *See* 42 U.S.C. § 262(i). Prior to the BPCIA, some biologics (e.g., human growth hormone) were reviewed by the FDA's Center for Drug Evaluation and Research ("CDER") rather than its Center for Biologics Evaluation and Research ("CBER"). Bob Carlson, *FDA: Change Is Good*, BIOTECHNOLOGY HEALTHCARE, Mar. 2004, at 27, 27. An interesting question for further research is whether the current binary division between CDER and CBER (and for that matter

focus and which represents most biotechnology drugs[32]—have structures determined by four different hierarchical organization levels[33] and can be modified in various ways through their synthesis by the living source.[34] As a consequence, the specific contours of manufacturing processes, including the selection of the host organism, the identification of a particular cell line, culture and media conditions, and purification procedures, all impact the characteristics and activity of the final product.[35] This Part first addresses the complex process of manufacturing biologics and its impact on the final biologic. Next, it considers the inadequacy of current techniques for characterizing the end product, and how that inadequacy interacts with path-dependent manufacturing. Third, it looks to the inadequate incentives for developing fundamental knowledge. Finally, it discusses the current regulatory framework for biosimilars.

A. *MANUFACTURING BIOLOGICS*

This Subpart considers the process of manufacturing biologics, as both the technical complexity and the path-dependence of this process are important for the competition and innovation issues with which we are concerned. Since certain technical details may be of interest to only a limited subset of readers, we have left many such details to the footnotes.

1. Path Dependence

Understanding the complexity of biologic manufacturing requires a brief, contrasting explanation of how small-molecule drugs are made. Small-molecule drugs are relatively simple chemical structures, generally made up of no more than several dozen atoms.[36] Once identified, the compound

---

between Hatch–Waxman and the BPCIA) will adequately address the spectrum of complexity going forward. That question is beyond the scope of this Article.

32. John Gar Yan Chan et al., *An Overview of Biosimilars*, 147 J. & PROC. ROYAL SOC'Y NEW SOUTH WALES 77, 77–78 (2014).

33. Proteins are characterized in increasing level of complexity by their primary amino acid sequence, secondary structure (i.e., the arrangement of amino acids into low-level structures, such as alpha helices and beta strands), tertiary structure (i.e., the arrangement of low-level structure into larger structures, such as beta barrels or zinc fingers, which can play specific functional roles), and quaternary structure (i.e., the interaction between different proteins or copies of the same protein to form a larger structure). CARL BRANDEN & JOHN TOOZE, INTRODUCTION TO PROTEIN STRUCTURE 3 (2d ed. 1999).

34. Paul J. Declerck, *Biologicals and Biosimilars: A Review of the Science and Its Implications*, 1 GENERICS & BIOSIMILARS INITIATIVE J. 13, 13 (2012).

35. *Id.*

36. Lipinski's Rule is used as a rough estimation of whether a molecule is suitable for use as an oral drug, assuming that the compound is biologically active. The Rule states that no more than one of five characteristics may be violated, and one characteristic is that the molecule be less than 500 Daltons in size. Christopher A. Lipinski et al., *Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings*, 23 ADVANCED DRUG

frequently can be made through any of several different chemical synthesis pathways.[37] Although the choice of chemical synthesis pathway may have an impact on manufacturing cost, it generally has little to no impact on the identity of the final product.[38] Small-molecule synthesis is well understood and the final products are usually quite pure with any impurities well characterized. No matter the pathway, the company knows what it has made and can confirm that the final product is essentially identical to the product of another company's different pathway.[39] This identity allows the introduction of generic small-molecule drugs via the Hatch–Waxman Act of 1984.[40]

Biologics, as opposed to small-molecule drugs, are typically far more path-dependent entities. Consider, for example, one of the first steps in process development for a biologic: selecting a cell line which will eventually produce the biologic. The details of cell line selection reveal both significant complexities and the presence of random, uncontrolled events.[41]

Cell line selection is an essentially random process. A starter population of cells is selected from among several possibilities (bacterial, yeast, or cells from mice or hamsters) and DNA encoding the protein of interest is added to the cells. This DNA is taken up in essentially random amounts.[42] To leverage this random distribution of both the number and location of gene copies, the cells are isolated, grown into populations, and evaluated for growth and production rates.[43] Further selection, with its own random elements, can help increase the number of copies, stability, and growth rate of the eventual final cell line.[44]

DELIVERY REVIEWS 3, 8–9 (1997). Biologics, on the other hand, are frequently more than 50,000 Daltons.

37. *See generally* 7 DANIEL LEDNICER, THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS (2008).

38. *Id.*

39. *See, e.g.*, FOOD & DRUG ADMIN. ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES SUBMITTED IN NDAS OR INDS—GENERAL CONSIDERATIONS (2014), http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm389370.pdf.

40. *Id.*

41. Aleš Berlec & Borut Štrukelj, *Current State and Recent Advances in Biopharmaceutical Production in* Escherichia coli, *Yeasts and Mammalian Cells*, 40 J. INDUS. MICROBIOLOGY & BIOTECHNOLOGY 257, 269 (2013).

42. In this process, known as transfection for mammalian cells and transformation for bacteria and non-animal eukaryotic cells, the recombinant DNA typically includes a gene encoding the therapeutic protein, a selection marker, and regulatory sequences. Feng Li et al., *Current Therapeutic Antibody Production and Process Optimization*, BIOPROCESSING J., Winter 2006, at 16, 16–17. Note that this process, too, relies on random mutation and copying: Cells only get more copies after the initial transfection from mutations that multiply the number of copies of the desired genes. But this mutation, too, is a random process.

43. *Id.* at 17.

44. Once promising cells have been identified, the number of copies can be increased by raising the concentration of selection marker inhibitor in the culture medium: Only cells with

Subsequent stages in manufacturing are also quite complex, as they turn on the interaction of the cell line with a complex environment. Once the culture medium is optimized (itself a process of some complexity),[45] cells are grown in large-scale vessels, making the biologic in a complex and variable production environment.[46] Once production is complete, the protein must be isolated and purified in several steps.[47]

2. Physiological Effects

This Article emphasizes these manufacturing details because final therapeutic proteins are influenced by each step in the manufacturing process. To take one well-studied example, the choice of organism from which to generate a cell line, and the culture conditions, can alter the pattern of carbohydrates attached to the surface of the protein, also known as the "glycosylation pattern."[48] Changes in glycosylation can significantly impact the biologic in several ways, including the stability of the protein (both outside and inside the body),[49] the length of time the protein remains with the bloodstream,[50] the binding of the protein to its therapeutic targets,[51] and the reaction of the body's immune system to the protein.[52]

For example, one study observed severe hypersensitivity in patients treated with Cetuximab, a monoclonal antibody used to treat metastatic colorectal cancer and squamous-cell carcinoma of the head and neck.[53] This hypersensitivity was based on the presence of a specific type of glycan attached to the protein, produced in mice but not in humans. The company had elected to make Cetuximab in a mouse cell line, and that early choice created

---

multiple copies of the resistance marker, and thus the biologic gene, can survive the increased inhibitor. *Id.*

45. *Id.* Note that in addition to the complexity of determining the best culture medium, the proteins used to feed the cells, usually digests from soy, wheat, or yeast, themselves, have a complex composition and may vary significantly from lot to lot. *Id.*

46. Throughout the growth process the cells are fed and maintained in an environment of monitored and dynamically changed temperature, pH, and other characteristics such as dissolved oxygen and carbon dioxide. *Id.* at 17–19.

47. *Id.* at 20–23. Purification can vary significantly depending on whether the cell produces the protein and excretes it into the culture medium or keeps the protein within itself; the latter possibility requires an additional step of breaking the cells apart. *Id.*

48. Huijuan Li & Marc d'Anjou, *Pharmacological Significance of Glycosylation in Therapeutic Proteins*, 20 CURRENT OPINION BIOTECHNOLOGY 678, 678–82 (2009). Maintaining consistent glycosylation is challenging as glycosylation patterns can change based on production system, production batch, and even over the course of a single production batch. Michael Butler, *Animal Cell Cultures: Recent Achievements and Perspectives in the Production of Biopharmaceuticals*, 68 APPLIED MICROBIOLOGY & BIOTECHNOLOGY 283, 286–88 (2005).

49. Li & d'Anjou, *supra* note 48, at 679.

50. *Id.* at 680–81.

51. *Id.* at 679–80.

52. *Id.* at 681–82.

53. *Id.*

a serious clinical issue once the biologic was actually used in patients.[54] Glycosylation is merely one type of variation known as post-translational modification, which are changes that happen after the protein's basic structure is formed. Manufacturing variation can lead to a plethora of such modifications and other alterations, with substantial clinical implications. Notable clinical effects include serious immunogenic reactions.[55]

B. INADEQUACY OF ANALYTICAL SCIENCE

The complexity and path-dependence of biologics manufacturing would be less important if analytical methods could characterize end-product biologics in sufficient detail to allow a determination of identity. However, in many cases, the state of analytical science at present and in the foreseeable future falls short of that goal.[56]

As discussed, biologics are highly variable, and such variability can have major impacts on a drug's safety and efficacy. Analytical methods could ease this problem by verifying that two different products were essentially identical in all relevant characteristics. In other words, even if manufacturing methods were different, the difference in manufacturing methods would matter less if the final products could be demonstrated to be identical. This approach works for small-molecule drugs. Indeed, the ease of proving product identity, independent of its manufacturing process, is what makes generic drugs under Hatch–Waxman possible.

However, although the issue is somewhat disputed, in many cases analytical methods available to biosimilar firms are insufficient to verify identity.[57] Although the analytical methods available are substantial, they cannot ensure that two proteins are identical.[58] Therefore, in order for a follow-on manufacturer to be confident that it has duplicated an originator firm's biologic, it must have knowledge of the originator firm's manufacturing process and cell lines.[59]

As noted, the extent to which biosimilar manufacturers can rely on analytical science is somewhat disputed. In a series of important articles, Mark McCamish, Head of Global Biopharmaceutical Development at Sandoz, and Gillian Woollett of Avalere Health have argued that analytical techniques have progressed to the point that biosimilar manufacturers should be able to prove similarity in the same way that originator manufacturers prove "comparability" in analyzing the consequences of their own process changes

54. *Id.*

55. *See* Steven A. Berkowitz et al., *Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars*, 11 NATURE REVIEWS DRUG DISCOVERY 527, 531–33 (2012).

56. *Id.*; *see also* FOOD & DRUG ADMIN. ET AL., *supra* note 30, at 4.

57. *See, e.g.*, Berkowitz et al., *supra* note 55; Huub Schellekens, Commentary, *How Similar Do 'Biosimilars' Need to Be?*, 22 NATURE BIOTECHNOLOGY 1357 (2004).

58. Berkowitz et al., *supra* note 55, at 527.

59. Schellekens, *supra* note 57, at 1358.

post-approval.[60] On this view, the FDA makes post-approval comparability determinations "extensively," and rarely requires intensive work (e.g., clinical trials) in these determinations.[61] Sandoz's views are particularly worthy of note, as it is the first firm to secure approval of a biosimilar application with the FDA (albeit on a relatively simple biologic, filgrastim (Neupogen)).[62]

Notably, however, Sandoz's application, as well as the FDA approval, ultimately relied heavily on clinical trials and the extensive European patient experience with the Sandoz product.[63] Similarly, as a recent FDA guidance document emphasizes, originator manufacturers can demonstrate to the FDA detailed knowledge of their manufacturing process—knowledge they have built up over many years.[64] In contrast, according to the FDA, "the manufacturer of a proposed [biosimilar] product is likely to have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) . . . and no direct knowledge of the [originator's] manufacturing process."[65] Therefore, the FDA believes "that more data and information will be needed to establish biosimilarity than would be needed to establish" comparability.[66]

C. *MISSING INCENTIVES FOR UNDERSTANDING*

This Article's discussion of the existing science relies on publicly available information. In some cases, originator firms (and, for that matter, biosimilar firms) may have developed more precise analytical methods, as well as more precise understandings about the effects of different manufacturing method changes. Originator firms have at least some economic incentive to develop

60. Mark McCamish & Gillian Woollett, *Worldwide Experience with Biosimilar Development*, 3 MABS, 209, 210–11 (2011) [hereinafter McCamish & Woollett, *Worldwide Experience*]; *see also* Mark McCamish & Gillian Woollett, *The State of the Art in the Development of Biosimilars*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 405, 408 (2012) [hereinafter McCamish & Woollett, *The State of the Art*] (noting that the frequency with which these determinations are made is not clear because FDA comparability determinations are not public).

61. McCamish &Woollett, *Worldwide Experience*, *supra* note 60, at 210.

62. In 2010, Sandoz had secured approval via the Hatch–Waxman pathway for a generic version of the complex non-biologic product Lovenox. *Id.* at 214. Similarly, Momenta Pharmaceuticals argues that its generic versions of the complex products Lovenox and Copaxone are essentially identical and that duplicating those products reflects greater challenges than duplicating a biologic. *Complex Generics*, MOMENTA PHARMACEUTICALS, http://www.momentapharma.com/pipeline/complex-generics.php (last visited Jan. 10, 2016). However, Momenta has not yet submitted any biosimilar applications in the United States, much less been approved. *Baxalta and Momenta Start Phase III Trial for Adalimumab Biosimilar*, GENERICS & BIOSIMILARS INITIATIVE ONLINE (Oct. 16, 2015), http://www.gabionline.net/Biosimilars/News/Baxalta-and-Momenta-start-phase-III-trial-for-adalimumab-biosimilar.

63. Ajaz S. Hussain, *Biosimilars in the USA: Is the EU Biosimilar Experience Advantage Good for the USA?*, LINKEDIN PULSE (Jan. 18, 2015), https://www.linkedin.com/pulse/biosimilars-usa-eu-biosimilar-experience-advantage-hussain-ph-d-.

64. FOOD & DRUG ADMIN. ET AL., *supra* note 30, at 5–6.

65. *Id.* at 6.

66. *Id.*

an understanding of manufacturing methods that reduces marginal manufacturing cost and reduces potential tort liability by improving quality. Biosimilar firms following the model advocated by Mark McCamish of Sandoz may have incentives to develop fundamental knowledge regarding analytical techniques.[67]

However, the available evidence indicates that the private sector's understanding of scientific fundamentals is underdeveloped. As noted above, FDA guidance documents state that the agency makes comparability determinations for originator manufacturers based in significant part on detailed knowledge of manufacturing process. Similarly, the FDA has testified before Congress about originators being unable "to fully measure structural differences that could be caused by changes in the manufacturing process."[68]

Additionally, as discussed further in Part IV.B, biologic originator manufacturers have themselves noted to Congress their concerns about being unable to predict, or even measure accurately, the creation of particles in their products that may provoke immune reactions. About a decade ago, this issue was brought to the fore by a prominent case involving the originator firm Johnson & Johnson and certain batches of its product Eprex, which was intended to address anemia by inducing creation of red blood cells but instead ended up inducing red blood cell death.[69]

Moreover, widely accepted economic models of basic research pioneered by Richard Nelson and Kenneth Arrow suggest that even firms that conduct substantial research and development might underinvest in fundamental understanding.[70] Although Nelson, Arrow, and others focus on basic research that is far removed from commercial application, their arguments also apply to fundamental understanding of work that has obvious commercial application—what Donald Stokes has famously called "use-inspired basic science."[71] In both cases, although fundamental understanding could have some advantages for the firm's internal operations (in this case by reducing manufacturing cost or improving quality), the full social value of such

---

67. *See* McCamish & Woollett, *The State of the Art*, *supra* note 60, at 411–12.

68. *The Potential Need for Measurement Standards to Facilitate the Research and Development of Biologic Drugs: Hearing Before the Subcomm. on Tech. & Innovation of the H. Comm. on Sci. & Tech.*, 111th Cong. 68–70 (2009) (statement of Steven Kozlowski, Director, Office of Biotechnology Prods., Office of Pharm. Sci., Ctr. for Drug Evaluation & Research, Food & Drug Admin.).

69. Sabine Louët, *Lessons from Eprex for Biogeneric Firms*, 21 NATURE BIOTECHNOLOGY 956, 956 (2003).

70. Kenneth J. Arrow, The Rand Corp., *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC AND SOCIAL FACTORS 609, 612 (Universities-National Bureau ed., 1962). *See generally* Richard R. Nelson, *The Simple Economics of Basic Scientific Research*, 67 J. POL. ECON. 297 (1959).

71. *See generally* DONALD E. STOKES, PASTEUR'S QUADRANT: BASIC SCIENCE AND TECHNOLOGICAL INNOVATION (1997).

understanding is likely to be captured only through broad use that has associated spillovers.[72]

Thus, an individual firm's return of investment in this fundamental research may be negative. For this reason, as discussed further in Part IV.B, the economic literature often looks favorably on research and development collaborations even between firms that are horizontal competitors.

This standard underinvestment story is bolstered by the regulatory context, which likely exacerbates underinvestment in fundamental understanding of how biologics work and are produced. With respect to small molecules, where significant fundamental understanding does exist, the FDA has been reluctant to allow manufacturers to implement this fundamental understanding to make changes once they have received market approval.[73] From the FDA's standpoint, once an originator firm has secured approval, the identity of the molecule is largely set, and any substantial change will typically demand further clinical trials.[74] In fact, detailed knowledge of manufacturing parameters sometimes leads to greater regulatory commitments: If a process can be controlled tightly, the FDA may then rigidly require such tight control, imposing additional burdens on the manufacturer.[75] To the extent that originators assume, based on the experience with small molecules, that fundamental understanding in the area of biologics will not ease their path in terms of making changes post-approval, they will underinvest in such understanding.

As for biosimilar firms, firms like Sandoz may be generating at least some fundamental knowledge about analytical characterization techniques. Public presentations by Sandoz on its biosimilar application for filgrastim have stressed the extensive array of analytical techniques the firm has used to

72. *But see* Wesley M. Cohen & Daniel A. Levinthal, *Absorptive Capacity: A New Perspective on Learning and Innovation*, 35 ADMIN. SCI. Q. 128 (1990) (arguing that firms may invest in research that has significant spillovers in order to attain "absorptive capacity"). In the legal literature, Edmund Kitch has gone in the opposite direction from Cohen. He has prominently analogized basic research to tangible property, and thereby argued that if a firm could be allowed an extremely broad patent on the basic research, it could capture full social surplus by exploiting certain uses of that patent internally and then licensing other uses. *See generally* Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265 (1977). While economists per se have generally not engaged Kitch's claim, an extensive law and economics literature disputes the claim. *See, e.g.*, Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990).

73. For a description of the effect of regulatory lock-in of idiosyncratic production choices on later manufacturing innovation in the small-molecule context, see W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 519–22 (2014).

74. *Id.*

75. *See* Norman Winskill, Vice President, Mfg., Pfizer, Inc., Testimony to the Food and Drug Administration Science Board Meeting (Nov. 16, 2001), http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3799t1_02.pdf.

demonstrate similarity.[76] As noted, however, filgrastim is a relatively simple biologic.[77] Moreover, Sandoz's application, and even more so the FDA advisory committee that recently approved the application, relied heavily on clinical trials and on the extensive European patient experience with the Sandoz product.[78]

D. THE CURRENT STATUTORY AND REGULATORY FRAMEWORK

The BPCIA reflects the inability of follow-on firms to produce true generic biologics. In the statute, Congress tried to ensure that follow-on biologics would be similar enough to achieve some of the efficiency and competitive advantages of generics.[79] The FDA, implementing the statute, has outlined the regulatory approach it will take to demonstrate biosimilarity.[80] The FDA's approach underscores the challenges faced by biosimilar manufacturers.

1. The Biologics Price Competition and Innovation Act

Congress passed the BPCIA in 2010 as Title VII of the Patient Protection and Affordable Care Act ("ACA").[81] In relevant part, it amended the Public Health Service Act to create a biosimilar pathway modeled to some extent after the Hatch–Waxman Act's generic drug approval pathway.[82] However, for the reasons discussed above, requiring that follow-on biologics meet the same standards as generics was judged infeasible. Instead, follow-on biologics may rely on the safety and efficacy data of the reference biologic if they are "highly similar" to the reference.[83]

To be "highly similar" under the BPCIA, there must be "no clinically meaningful differences . . . in terms of the safety, purity, and potency."[84] Beyond biosimilarity, a follow-on may be found "interchangeable" with its reference product, the original biologic, if it is shown that: (1) the biosimilar will have the same clinical effect as the reference biologic for every individual patient; and (2) for biologics administered more than once (as most biologics are), switching between the reference biologic and the biosimilar poses no

---

76. MARK MCCAMISH, ZARXIO™ (FILGRASTIM): SANDOZ, A NOVARTIS COMPANY: PRESENTATION TO THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (2015), http://www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM431119.pdf.

77. *See supra* note 11.

78. Hussain, *supra* note 63.

79. This Article focuses on the U.S. regime, but the situation is similar elsewhere; the U.S. law is modeled on the E.U.'s biosimilar regime, and other countries have adopted this approach.

80. *See infra* Part II.D.2.

81. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111–148, §§ 7001–03, 124 Stat. 804–21 (2010) (codified as amended at 42 U.S.C. § 262 (2012)).

82. *Id.*

83. 42 U.S.C. § 262(i)(2)(A).

84. *Id.* § 262(i)(2).

additional safety or efficacy risk compared to the use of the reference product alone.[85]

For purposes of price reduction, an interchangeable follow-on represents the closest parallel to a generic small-molecule drug. The BPCIA provides that pharmacists may automatically substitute such interchangeables for originator biologics, just as generic small-molecule drugs are automatically substituted for brand-name drugs.[86] However, for the reasons discussed above, absent follow-on access to manufacturing details, achieving interchangeability is highly unlikely.[87]

2. FDA Implementation

The statutory approach described above is quite broad, but the FDA's implementation is significantly more detailed. Although the FDA has not promulgated regulation,[88] it has issued multiple draft guidances on the biosimilar approval pathway, and in particular what needs to be demonstrated to show biosimilarity.[89]

Notably, the FDA has eschewed a rigid structure for demonstrating biosimilarity in favor of a risk-based, case-by-case, totality-of-the-evidence approach.[90] This flexibility contrasts with the agency's rigid stance post-approval discussed in Part II.C, and is discussed in Part V.

Under the FDA's approach, demonstrating biosimilarity requires a stepwise decrease in risk and uncertainty as characterization of the follow-on biologic progresses through several stages, moving from structural and functional analysis through animal data and finally human clinical data on pharmacology, immunogenicity, and potentially safety and efficacy if

85. *Id.* § 262(i)(3), (k)(4).

86. Falit et al., *supra* note 12, at 298.

87. *See supra* Part II.B.

88. In general, the FDA operates in significant part through guidance, a practice that has drawn severe criticism from some scholars. *See* Lars Noah, *Governance by the Backdoor: Administrative Law(lessness?) at the FDA*, 93 NEB. L. REV. 89, 90 (2014). Although guidance does not provide binding law, it does allow for greater agency flexibility in cases where knowledge is rapidly evolving. *See infra* Part V.

89. *See, e.g.*, FOOD & DRUG ADMIN. ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., BIOSIMILARS: ADDITIONAL QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009: GUIDANCE FOR INDUSTRY (Rev. 1, 2015), http://www.fda.gov/downloads/Drugs/. . ./Guidances/UCM273001.pdf; FOOD & DRUG ADMIN. ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY (2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM397017.pdf; FOOD & DRUG ADMIN. ET AL., *supra* note 30; FOOD & DRUG ADMIN. ET AL., U.S. DEP'T OF HEALTH & HUMAN SERVS., QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A THERAPEUTIC PROTEIN PRODUCT TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY (2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.

90. FOOD & DRUG ADMIN. ET AL., *supra* note 30, at 8.

needed.[91] Throughout, the process emphasizes decreasing the risk and uncertainty that remain from limitations of the prior step. The final step is clinical trials to demonstrate that whatever uncertainty remains from characterization has minimal effects on patients.[92]

III. PROCESS DETAILS AS TRADE SECRETS: THE NORMATIVE ANALYSIS

This Part will discuss in detail the efficiency losses, static and dynamic, associated with current trade secrecy practices in biologics manufacturing. To set the stage for the normative discussion, this Part begins with a general overview of basic patent and trade secret doctrine and of the economics of trade secrecy. The general overview does not fully apply to manufacturing process information submitted to the FDA. Nonetheless, it provides important context.

A. PATENT AND TRADE SECRET DOCTRINE

Boilerplate patent law holds that firms must choose between having a patent on an inventive product or process and keeping it a trade secret. Patent law's disclosure requirement is reflected both in the text of the patent statute and in case law.[93]

---

91. *See id.* at 9–17. Structural analysis measures the physical characteristics of the protein, and faces the limitations described above. *Id.* at 9. Functional analysis evaluates the performance of the product compared to the reference product in *in vitro* assays such as "biological assays, binding assays, and enzyme kinetics." *Id.* at 10. Animal data on toxicity can help demonstrate safety; animal studies on pharmacodynamics (how the drug acts on the body) and pharmacokinetics (how the body metabolizes the drug) can help demonstrate similarity to the reference product, and animal immunogenicity studies can demonstrate differences between the reference and follow-on even though they poorly predict human immune responses. *Id.* at 11–12.

92. At least one challenge with the approach of using clinical trials as the final arbiter of similarity parallels the growing recognition that clinical trials are generally too small and too short to evaluate negative effects of drugs that may only arise in the longer term or in limited populations. *See* Timothy Brewer & Graham A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281 JAMA 824, 824 (1999). Post-market surveillance is the preferred approach to deal with these issues. *Id.* If, however, biosimilars differ in ways that would only be noticed in post-market surveillance—as seems likely, based on the path-dependence differences described above, *see supra* Part II.B—then surveillance of the reference product will not help avoid those problems. Of course, to the extent that interchangeables became possible, surveillance of the reference product would suffice.

93. 35 U.S.C. § 112(a) (2012) (requiring that a patent "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same, and . . . set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention"). The Court of Appeals for the Federal Circuit, which hears all appeals in patent cases, has held that this section contains both a requirement to "describe" the invention in structural terms and to enable the invention. Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010). Although the written description and enablement requirements are similar, they are not identical. *See id.* ("[A]lthough written description and enablement often rise and fall together, requiring a written description of the invention plays a vital role in curtailing claims that do not require undue experimentation to make and use, and thus satisfy enablement,

While disclosure's doctrinal foundation is clear, the extent to which this goal is normatively central to patent law remains contested. Scholars have argued both for[94] and against[95] its centrality.[96] Additionally, the extent to which patents practically aid the spread of knowledge remains a contested empirical question. Although the answer likely varies across areas of scientific and technological inquiry, the majority view is that disclosure is often inadequate.[97] This inadequacy may be a function of current legal requirements or of the inability of current patent institutions to enforce these requirements.

This Article does not take a view on whether patent law generally should take disclosure as a central normative goal. Rather, it makes the case that greater disclosure of biologic manufacturing processes is likelyto improve efficiency substantially, both static and dynamic. Whether greater disclosure should be achieved through the patent system or through other mechanisms is a question to which this Article turns in Part IV.

In the remainder of this Part, this Article makes a detailed case for why trade secrecy is often privately valuable but only socially valuable in certain cases. In the case of biologics manufacturing, indefinite trade secrecy is on balance socially deleterious.

---

but that have not been invented, and thus cannot be described."). In contrast with enablement, which primarily serves the disclosure function, written description also serves a notice function.

94. *See, e.g.*, Dan L. Burk, *The Role of Patent Law in Knowledge Codification*, 23 BERKELEY TECH. L.J. 1009, 1012 (2008) ("[M]any familiar provisions of the patent statute may be viewed as incentives for codification of otherwise tacit knowledge . . . ."); Jeanne C. Fromer, *Patent Disclosure*, 94 IOWA L. REV. 539, 542 (2009) (Arguing for disclosure's "centrality in the patent system"); Sean B. Seymore, *The Teaching Function of Patents*, 85 NOTRE DAME L. REV. 621, 627 (2010) (arguing for strong disclosure and that "[i]t is now time to transform the patent into a readable teaching document").

95. *See, e.g.*, Alan Devlin, *The Misunderstood Function of Disclosure in Patent Law*, 23 HARV. J.L. & TECH. 401, 403 (2010) ("[D]isclosure is both ineffective and potentially poisonous to larger social goals."); Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. REV. 123, 146 (2006) ("[D]isclosure obligations [are] inconsistent with the theoretical justifications of patent law . . . ."); Mark A. Lemley, *The Myth of the Sole Inventor*, 110 MICH. L. REV. 709, 745 (2012) ("Disclosure theory cannot . . . support the modern patent system.").

96. For a useful review of scholarly views in this area, see Lisa Larrimore Ouellette, *Do Patents Disclose Useful Information?*, 25 HARV. J.L. & TECH. 545, 546–47 (2012). Ouellette suggests that rather than questioning disclosure's value as a rationale for a patent system, its value should be examined taking the system as a given; that is, since a patent system exists, what is the value of disclosure requirements, and is that value sufficient? *Id.* at 548.

97. *See, e.g.*, Subhashini Chandrasekharan et al., *Proprietary Science, Open Science and the Role of Patent Disclosure: The Case of Zinc-Finger Proteins*, 27 NATURE BIOTECHNOLOGY 140 (2009) (discussing lack of disclosure in the context of zinc-finger protein patents); Mark A. Lemley, *Ignoring Patents*, 2008 MICH. ST. L. REV. 19, 22 n.16 ("Empirical research suggests that scientists don't in fact gain much of their knowledge from patents, turning instead to other sources.").

B. THE ECONOMICS OF TRADE SECRECY: GENERAL CONSIDERATIONS

In general, as various surveys have shown, manufacturing firms across different industries frequently use secrecy to protect both product and process information.[98] Secrecy appears particularly useful for processes.[99] This differential value arises from the challenges in detecting process patent infringement and, in some cases, the difficulty of reverse engineering.

Although secrecy clearly confers private value to the company, scholars have debated the extent to which such secrecy should be encouraged through the apparatus of trade secret law, now adopted by 47 states through the mechanism of the Uniform Trade Secrets Act ("UTSA").[100] Under the UTSA, the definition of what constitutes a trade secret is broad—any information that derives actual or potential economic value from "not being readily ascertainable" and which is the subject of measures "reasonable under the circumstances to maintain its secrecy" is included.[101]

In a prominent series of articles starting in 1998, Professor Robert Bone has argued that any protection against rent-dissipating "secrecy arms races" provided by trade secrecy law is outweighed by its disadvantages.[102] Bone argues that unlike patent law, trade secrecy encourages duplicative effort and retards cumulative innovation.[103]

Other scholars have countered that trade secrecy creates incentives to innovate in those contexts where an invention does not meet the standards for patent validity or where seeking and enforcing a patent (particularly given the well-known practical limitations of the patent system) would be

---

98. *See* Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)* 10 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000) (finding, based on survey of R&D managers of manufacturing firms administered in the United States in 1994, that across industries secrecy was more effective than patents for both product and process inventions); *see also* John E. Jankowski, *Business Use of Intellectual Property Protection Documented in NSF Survey*, INFOBRIEF (Nat'l Ctr. for Sci. & Eng'g Statistics), Feb. 2012, at 5 (finding that in 2008, more than 50% of businesses "with R&D activity" rated secrecy very important or somewhat important).

99. *See* Cohen et al., *supra* note 98, at 10 (noting that secrecy was reported to be the most effective strategy for protecting process innovations).

100. *The Uniform Trade Secrets Act (UTSA)*, NDAS FOR FREE, http://www.ndasforfree.com/UTSA.html (last visited Jan. 10, 2016) (listing states adopting the UTSA). Only New York, Massachusetts, and North Carolina have not adopted the UTSA. *Id.*

101. UNIF. TRADE SECRETS ACT § 1(4) (NAT'L CONFERENCE OF COMM'RS ON UNIF. STATE LAWS 1986) (amended 1985).

102. *See, e.g.*, Robert G. Bone, *Exploring the Boundaries of Competitive Secrecy: An Essay on the Limits of Trade Secret Law*, *in* 13 LAW, INFORMATION AND INFORMATION TECHNOLOGY 99 (Eli Lederman & Ron Shapira eds., 2001); Robert G. Bone, *A New Look at Trade Secret Law: Doctrine in Search of Justification*, 86 CALIF. L. REV. 241 (1998) [hereinafter Bone, *A New Look*]; Robert G. Bone, *The (Still) Shaky Foundations of Trade Secret Law*, 92 TEX. L. REV. 1803 (2014) [hereinafter Bone, *The (Still) Shaky Foundations*]; Robert G. Bone, *Trade Secrecy, Innovation, and the Requirement of Reasonable Secrecy Precautions*, *in* THE LAW AND THEORY OF TRADE SECRECY: A HANDBOOK OF CONTEMPORARY RESEARCH 46 (Rochelle C. Dreyfuss & Katherine J. Strandburg eds., 2011).

103. Bone, *A New Look*, *supra* note 102, at 266–67.

prohibitively costly.[104] The prominent Carnegie Mellon survey on manufacturing firms' strategies for appropriability of intellectual assets indicates that, at least as of 1994 (when the survey was conducted), these arguments had merit.[105] Respondents to that survey stated that difficulty demonstrating novelty and application cost represented reasons not to patent.[106]

Proponents of trade secrecy also argue that trade secrecy law offers a robust mechanism for overcoming Arrow's information paradox and fostering licensing markets that result in cumulative innovation.[107] Although this argument seems plausible in principle, its empirical foundation is unclear. Although scholars who study technology licensing empirically have argued that *patent* licensing markets provide a vehicle by which relevant trade secret knowledge is transferred,[108] they have not suggested the existence of robust markets for such knowledge independent of the underlying patent.

When played out across many different types of invention, these debates over the comparative social value of trade secrecy can be very difficult to parse, let alone ground empirically.[109] Additionally, these abstract debates tend not to account for the incentives of codification and other policy considerations relevant to trade secrecy in heavily regulated industries. For these industries, the common law UTSA is much less relevant than the regulatory architecture set up by the Freedom of Information Act, the Trade Secrets Act, and the agency's organic statute.[110]

This Article addresses this debate in a specific inventive and regulatory context—that of trade secrecy with respect to details of biologics manufacturing.[111] In this context, the information in question has tremendous value, both private and social. However, private value is realized in a regime—trade secrecy—that creates very significant problems for purposes of realizing social value.

---

104. *See, e.g.*, Mark A. Lemley, *The Surprising Virtues of Treating Trade Secrets As IP Rights*, 61 STAN. L. REV. 311 (2008); Michael Risch, *Why Do We Have Trade Secrets?*, 11 MARQ. INTELL. PROP. L. REV. 1 (2007).

105. *See generally* Cohen et al., *supra* note 98.

106. *See id.* at fig.5.

107. Arrow's information paradox highlights the peculiar status of information: It is valuable only when disclosed but also (absent mechanisms like intellectual property) loses its private value when disclosed. *See* Arrow, *supra* note 70, at 614–16; *see also* Lemley, *supra* note 104, at 336 (arguing that trade secrecy may allow firms to overcome Arrow's information paradox).

108. *See generally* ASHISH ARORA ET AL., MARKETS FOR TECHNOLOGY: THE ECONOMICS OF INNOVATION AND CORPORATE STRATEGY (2001). The fact that trade secret knowledge necessary to practice the patent would need to be transferred through a license of course calls into question the comprehensiveness of the patent disclosure.

109. *See generally* Bone, *The (Still) Shaky Foundations*, *supra* note 102.

110. *See infra* Part III.C.

111. For a discussion in other specific contexts, see, for example, Chandrasekharan et al., *supra* note 97; Ouellette, *supra* note 96.

C. TRADE SECRETS IN THE BIOLOGICS MANUFACTURING CONTEXT

1. The Private Value of Trade Secrecy

In the 1994 Carnegie Mellon survey, as well as a 2008 NSF survey, the biopharmaceutical manufacturing sector indicated significant reliance on trade secrecy, particularly in the context of manufacturing processes; indeed, in 1994, trade secrecy for biopharmaceutical manufacturing processes was rated nearly twice as effective as patents.[112] These surveys do not distinguish small-molecule manufacturing and biologics manufacturing. However, as a logical matter, the regulatory requirement that follow-on manufacturers essentially reverse engineer the originator's process,[113] coupled with the difficulty of doing so, presumably make trade secrecy over the details of biologics manufacturing extremely valuable. These process details include characteristics of the vector and cell line used, cell line growth conditions, and purification processes.[114]

To be sure, biologics firms typically seek extensive composition-of-matter patent protection.[115] However, in keeping with scholars' suspicions of the practical value of patent disclosure, composition-of-matter patents do not generally provide follow-on firms details regarding manufacturing process. Even in cases where biopharmaceutical firms file process patents, these patents are less than fully revealing. For example, in 2006, a decade after it filed the key product patent on its anti-TNF antibody Humira,[116] the originator firm Abbott (now Abbvie) filed a patent application on methods for improving anti-TNF antibody expression through improvements in cell culture media, which evolved into several patents.[117] However, because these patents obviously cover only one portion of the process, their value in terms

---

112. Cohen et al., *supra* note 98, tbl.2.

113. *See supra* Part II.C.

114. *See supra* Part II.

115. *See, e.g.*, Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?* 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012). Although the fact of extensive protection is known, the full scope and characteristics of this patent protection are not easy to determine. Unlike Hatch–Waxman, which sets up an FDA-administered registry known as the Orange Book onto which originator firms place patents that "could reasonably be asserted" against a generic competitor, BPCIA does not set up a patent registry. *See* 42 U.S.C. § 262(*l*)(1)(D) (2012). Instead it enunciates a highly complex set of procedures though which originator and follow-on firms exchange information regarding patents. *See id.* 262(*l*). Follow-on firms planning to enter with biosimilar products must "slog through" a variety of databases, proprietary and nonproprietary. E-mail from Shashank Upadhye, former Vice President & Glob. Head of Intellectual Prop., Apotex, to Arti K. Rai (June 9, 2014, 1:37 PM) (on file with authors).

116. The key product patent (patent number 6,090,382) was filed in February 1996. Human Antibodies That Bind Human TNFα, U.S. Patent No. 6,090,382 (filed Feb. 9, 1996).

117. *See, e.g.*, Dual Variable Domain Immunoglobins and Uses Thereof, U.S. Patent No. 8,735,546 B2 (filed Aug. 2, 2011); Methods of Producing Anti-TNF-Alpha Antibodies in Mammalian Cell Culture, U.S. Patent No. 8,663,945 B2 (filed Nov. 30, 2011).

of disclosure was limited. For this reason, as discussed earlier, follow-on firms must essentially reverse engineer processes.[118]

Going forward, from a private value standpoint, it is possible that the BPCIA's regulatory procedure for exchange of patent information may make originator process patents easier to enforce than the ordinary process patent and thus more attractive. As noted in the Introduction, the procedure facilitates identification of infringement by the follow-on applicant by setting up a procedure through which the follow-on firm discloses the contents of its FDA application to the originator. As with the originator application, this application reveals details of the manufacturing process.

On the other hand, the highly confused nature of the law interpreting the patent statute's "safe harbor" for patent infringement in the context of regulatory submissions may make manufacturing method patents unattractive.[119] In two recent opinions, the Federal Circuit has reached arguably divergent conclusions regarding the extent to which infringement of patents in the context of generating information collected for purposes of compliance with FDA regulatory processes falls under the safe harbor.[120]

Other aspects of the legal and regulatory scheme surrounding manufacturing processes affirmatively enhance the private value of trade secrecy. Although an originator firm's manufacturing process forms the template against which the FDA judges all biosimilar applicants, current federal statutory law appears strictly to bar any revelation of originator process details by the FDA. Both the D.C. Circuit and Tenth Circuit Court of Appeals have interpreted the relevant statutes (the Freedom of Information Act and the Trade Secrets Act) to encompass as a trade secret "a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities."[121] Moreover, although the Trade Secrets Act does allow agencies to release trade secrets to the extent that such release is "authorized by law,"[122] other statutory law

118. Additionally, in a significant number of cases, patents *cannot* contain all relevant information. As discussed further in Part IV, patents are typically filed at the beginning of clinical trials, and the manufacturing process is often altered over the course of these trials.

119. Broadly speaking, under the safe harbor provisions, firms using patented technology to prepare for a required FDA filing are immune from patent infringement suits based on that conduct. 35 U.S.C. § 271(e)(1) (2012).

120. *See, e.g.*, Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1359–61 (Fed. Cir. 2012) (holding that the safe harbor provision applied to manufacturing method patent, even post-approval); Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1072 (Fed. Cir. 2011) (holding that the safe harbor provision did not apply to post-approval activity).

121. Pub. Citizen Health Research Grp. v. Food & Drug Admin., 704 F.2d 1280, 1288 (D.C. Cir. 1983); *accord* Anderson v. Dep't of Health & Human Servs., 907 F.2d 936, 944 (10th Cir. 1990); *see also* CNA Fin. Corp. v. Donovan, 830 F.2d 1132, 1151–52 (D.C. Cir. 1987) (holding that Exemption 4 of FOIA determines not only what the federal government must release in response to a FOIA request but also what the Trade Secrets Act allows the government to release).

122. In relevant part, the text of the Trade Secrets Act reads:

doesn't confer any clear affirmative authority. To the contrary, section 331(j) of the FDA's organic statute prohibits the agency from releasing to the public information "concerning any method or process which as a trade secret is entitled to protection."[123]

For these reasons, while trade secrecy is quite attractive from a private standpoint, greater disclosure is likely to have significant social value.

2. The Social Value of Disclosure

Most straightforwardly, disclosure would significantly reduce the amount of largely duplicative research that follow-on researchers must do. As discussed in Part II, the current state of analytical science is such that even innovator firms cannot use analytic techniques to guarantee absolute identity of molecule between batches. Instead, an innovator manufacturer must demonstrate "consistency in manufactur[ing], with attributes that fall within a set of acceptable specification criteria that regulators have agreed to through a history of testing and characterization."[124]

In contrast with originator firms and regulators, follow-on firms do not have access to this detailed prior knowledge of manufacturing processes. Rather, to create a biosimilar, the developing company attempts to reverse engineer the manufacturing process of the reference product.[125] In some

---

> Whoever, being an officer or employee of the United States or of any department or agency thereof, . . . publishes, divulges, discloses, or makes known in any manner or to any extent *not authorized by law* any information coming to him in the course of his employment or official duties . . . which information concerns or relates to the trade secrets . . . of any person, firm, partnership, corporation, or association . . . shall be fined under this title, or imprisoned not more than one year, or both; and shall be removed from office or employment.

18 U.S.C. § 1905 (2012) (emphasis added).

123. 21 U.S.C. § 331(j) (2012). Section 355(i) of the Food, Drug, and Cosmetics Act does give the FDA expansive authority to impose on regulated parties "other conditions" that "relat[e] to the protection of the public health." 21 U.S.C. § 355(i)(1). Moreover, in January 2001, the FDA did rely in part on this authority to propose disclosure rules with respect to human gene therapy clinical data. *See* Rebecca S. Eisenberg, *Data Secrecy in the Age of Regulatory Exclusivity* 467, 479 *in* THE LAW AND THEORY OF TRADE SECRECY: A HANDBOOK OF CONTEMPORARY RESEARCH, *supra* note 102. Indeed, many of the same innovation arguments we engage in this Article have been used by advocates of greater clinical trial data disclosure. *See generally* COMM. ON STRATAGIES FOR RESPONSIBLE SHARING OF CLINICAL TRIAL DATA, INST. OF MED. OF THE NAT'L ACADS., SHARING CLINICAL TRIAL DATA: MAXIMIZING BENEFITS, MINIMIZING RISK (2015) (collecting references). However, subsection (j) appears to single out process details as a different type of information than clinical trial data. 21 U.S.C. § 331(j).

124. Berkowitz et al., *supra* note 55, at 529.

125. Telephone Interview with Bruce Leicher, Vice President & Gen. Counsel, Momenta Pharm. (Oct. 18, 2012). Although Momenta has demonstrated very high levels of expertise in this area by winning approval of generic versions of the complex mixtures Lovenox and Copaxone, its success hinges on better reverse engineering of manufacturing, not on simply understanding the resulting product and matching it.

cases, this reverse engineering is impossible.[126] Even in those cases where it is possible, it is very expensive.[127] Moreover, the biosimilar may direct its work towards duplicating idiosyncratic choices made by the reference sponsor.[128] This path-dependence restricts the development of biosimilars for reasons unconnected with the safety and efficacy of the biologic.

One counterargument is that the development of greater reverse-engineering expertise, and potentially greater analytical capabilities used for that reverse engineering, may itself be a useful form of innovation. This argument has some validity, particularly with respect to development of analytical capabilities. As noted, however, the relatively narrow focus on choices made by the originator limits the larger social benefit from the reverse engineering.

Current estimates indicate that repeating clinical trials in order to show biosimilarity or interchangeability is likely to cost as much as $100 million to $250 million.[129] In comparison, the cost of completing bioequivalence studies for a small molecule can be as low as $1 million to $2 million.[130] Because of this very significant barrier to entry, true generic competition in biologics will, at least for the foreseeable future, be difficult to achieve. Instead, as a prominent FTC report that analyzed the issue concluded, competition from biosimilar and even interchangeables may resemble competition between branded biologics.[131] With two or three biosimilar entrants, prices may decrease by 10–30%.[132] Notably, the FTC predictions are roughly in line with the price reductions biosimilars have generated in Europe.[133]

Additionally, greater disclosure would foster cumulative innovation, and could catalyze work into the aspects of biologics manufacturing that are most unpredictable and thus would benefit most greatly from improved knowledge. Increased disclosure would also enhance nascent public-private efforts to produce fundamental knowledge about biologics manufacturing. As discussed in Part II.C, current incentives to produce this fundamental knowledge are far from socially optimal.

The challenge lies in generating greater disclosure and fundamental knowledge without inappropriately reducing originator incentives to innovate. Part IV discusses this important challenge at length and considers policy prescriptions.

---

126. *Id. See generally* Berkowitz et al., *supra* note 55.

127. Telephone Interview with Bruce Leicher, *supra* note 125.

128. *Id. See generally* Walsh, *supra* note 15.

129. Walsh, *supra* note 15, at 995.

130. H. Grabowski et al., *Biosimilars, in* 1 ENCYCLOPEDIA OF HEALTH ECONOMICS 86, 90 (Anthony J. Culyer ed., 2014).

131. FED. TRADE COMM., EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 13 (2009).

132. *Id.* at 23.

133. Megerlin et al., *supra* note 18, at 1806.

IV. POLICY PRESCRIPTIONS

This Part turns to policy prescriptions for addressing the secrecy problem. Policymakers could use mandates or incentives to elicit information from originator firms, implemented either through the patent system or FDA's regulatory system. Additionally, public funding of manufacturing research, coupled with greater standardization of manufacturing methods, could help solve the problem of secret methods.

A. DISCLOSURE THROUGH REGULATORY LEVERS

Incentives or mandates for firms to disclose their manufacturing methods could operate in one of two ways: (1) through the patent system; or (2) by tying disclosure to regulatory approval and oversight of biologics. This Subpart discusses both options, concluding that FDA regulatory approval provides the better institutional setting.

1. Patent Disclosure

The patent statute requires disclosure sufficient to show the ordinary scientist working in the field how to "make and use" the invention claimed.[134] As a doctrinal matter, patents might therefore seem a logical locus for potential disclosure reform. In the context of biologics patent applications, however, disclosure is ineffective for at least two reasons. First, as with other patent applications, the U.S. Patent and Trademark Office ("PTO") may not have sufficient resources or expertise to monitor effective disclosure.[135] Second, and more conceptually, any disclosure made by the originator biologic firm at the time it files its patent application may have only partial overlap with the disclosure needed by a follow-on biosimilar manufacturer (or, for that matter, with the disclosure needed to stimulate cumulative innovation). This is because biologics patent applications are typically filed before clinical trials begin, so the biologic product and its associated process that are ultimately approved by the FDA will likely have been altered by the time it is approved.

Consider, for example, the principal patent on the blockbuster biologic Enbrel. This patent describes expressing the protein in any of at least eight bacterial strains, yeast, and at least ten different cell culture types from multicellular organisms including hamsters, monkeys, and humans.[136] Indeed, the patent mentions at least 20 different possibilities for expressing the protein in yeast alone.[137] And while the patent does describe specific

134. 35 U.S.C. § 112(a) (2012).

135. *See, e.g.*, Arti K. Rai, *Improving (Software) Patent Quality Through the Administrative Process*, 51 HOUS. L. REV. 503 (2013).

136. DNA Encoding a Chimeric Polypeptide Comprising the Extracellular Domain of TNF Receptor Fused to IGG, Vectors, and Host Cells, U.S. Patent No. 5,447,851 (filed Apr. 2, 1992).

137. *Id.*

examples—likely those used in the discovering laboratory—it notes that "those of skill will appreciate that the following examples are intended to be exemplary only and that numerous changes, modifications and alterations can be employed without departing from the spirit and scope of the invention."[138] Pfizer undoubtedly uses such modifications in the commercial manufacture of Enbrel, but the nature, extent, and effect of those modifications is completely unknown. And, as described above, precise variations in manufacturing methods can have significant clinical impacts.[139] Thus, from a large menu of possibilities—and, indeed, from similar possibilities not specifically mentioned—a much smaller subset matches the FDA's definition of biosimilarity.[140]

The Enbrel patent disclosure thus exemplifies both problems noted above. The first problem is the PTO's decision to allow such a broad patent. Arguably, as Dmitry Karshtedt has suggested, because biologics cannot be described precisely by structure, the only composition-of-matter patents that should be allowed on biologics are so-called product-by-process patents.[141] These patents are essentially process patents, as the patentee's coverage is limited to the particular method it has used.[142] However, a product-by-process patent filed at the time when clinical testing began might well discuss a process different from the process Pfizer and the FDA ultimately chose for commercial manufacture. Not only would the patent's disclosure be unhelpful to biosimilar firms, but the patent itself would fail to protect Pfizer's biologic.

In order to channel a more robust biologic disclosure through the patent system, patent law might allow pioneer firms to seek broad patent protection at the outset (e.g., along the lines of the Enbrel patent,) but condition the patent's continued validity on an updated disclosure that enabled one skilled in the art to make the biologic to the specifications identified in any Biologics Licensing Application ("BLA") covering the patented biologic.[143] Thus, when a firm received a BLA on its patented biologic, it would need to supplement the patent disclosure with whatever information was necessary to ensure that competitors could actually make a biosimilar once the patent expired. More broadly, patent law could require that, for any patented product or process that is subject to regulatory approval, the patent disclosure must be so

138. *Id.*

139. *See supra* Part II.A.

140. *See supra* Part II.D.2.

141. Karshtedt, *supra* note 25, at 139.

142. *Id.*

143. Some complications might arise when the patentee and the BLA sponsor are different entities, though typically the BLA sponsor would be expected to be either the owner, assignee, or exclusive licensee of a patent covering the sponsored biologic.

supplemented.[144] The expert regulatory agency in question (here the FDA) could police the supplementary disclosure, presumably with greater efficacy than the PTO.[145]

Although the patent statute currently contains no mechanism for mandatory supplementation, legislative implementation of such a mechanism would force firms to choose between patents and maintaining secrecy over production methods. That is, legislation could force actual implementation of the boilerplate requirement that firms must choose between patents and trade secrecy.

Whether this approach would actually promote enough disclosure is a harder question. Frequently, the choice might be an easy one with no benefit from disclosure. Given the current 12-year regulatory exclusivity for biologics clinical trial data, firms might rely on that exclusivity and simply forgo patenting.[146] In that case, no disclosure would be forthcoming. Congress could, of course, shorten the regulatory exclusivity term, thereby making patents more attractive. However, as various scholars have now noted, regulatory exclusivity incentives are much more precisely tailored than the patent regime for products that require large research and development investment precisely because of regulatory requirements.[147]

Overall, channeling a meaningful disclosure requirement for biologic manufacturing through the patent system has the potential to accelerate biosimilar development. However, the discrepancy between what is required to make a regulated product and what is required to make an earlier version on which patent protection is sought suggests that locating a robust disclosure

---

144. The absence of an Orange-Book-style registry of patents covering licensed biologics makes this endeavor more complicated than a hypothetical analogous pharmaceutical regime. This difficulty might be overcome by integrating the patent-exchange mechanism described in the BPCIA; a sponsor could be required to certify that any patents listed in the BPCIA "patent dance" were appropriately supplemented at the time of the BLA's grant. *See infra* notes 149–51.

145. Interestingly, the U.S. Code currently contains a provision calling for the FDA to assist the PTO in ordinary examination of drug patent applications:

> The Secretary [of Health and Human Services] is authorized and directed, upon request from the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, to furnish full and complete information with respect to such questions relating to drugs as the Director may submit concerning any patent application. The Secretary is further authorized, upon receipt of any such request, to conduct or cause to be conducted, such research as may be required.

21 U.S.C. § 372(d) (2012). To our knowledge, this provision has never been utilized.

146. Yaniv Heled has argued that firms should be required to choose between exclusivity and patent protection in any case. *See generally* Heled, *supra* note 115. The proposal here would create a similar choice, though indirectly.

147. *See generally* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007); Arti K. Rai, *Building a Better Innovation System: Combining Facially Neutral Patent Standards with Therapeutics Regulation*, 45 HOUS. L. REV. 1037 (2008); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503 (2009).

requirement within the FDA regulatory oversight structure is the better option.

2. Disclosure Through the FDA Regulatory Structure

Public disclosure of precise and enabling manufacturing methods could be made a condition of FDA approval (in a mandate-based version) or could be incentivized with an additional period of FDA-enforced regulatory exclusivity (in an incentive-based version). Because the FDA already serves as the gatekeeper for regulatory approval, and already has the necessary expertise to evaluate disclosure of biologic characteristics and manufacturing methods, it could ensure that manufacturers actually disclose the relevant information.

This assurance would be especially strong if the public disclosure were the same as the disclosure to the FDA—that is, if the Chemistry and Manufacturing Controls ("CMC") section of the BLA were publicly disclosed upon BLA approval. Under such a requirement, the sponsor's interest in disclosing inadequately to limit eventual competition would be countered by its interest in disclosing fully to win FDA approval to enter the market in the first place.[148]

Disclosure linked to the CMC would also address any objection that transmission of trade secret-based knowledge would be excessively burdensome because the knowledge in question is tacit, not codified. In this case, the CMC requirement already mandates knowledge codification.

There is some precedent for legislation promoting disclosure of manufacturing methods linked to regulatory approval—though the existing disclosure regime is one-way, circumscribed, and in the opposite direction. As noted above, the BPCIA sets up a complex system of patent exchange for the purpose of facilitating patent enforcement when a biosimilar application is filed.[149] As part of this mechanism, within 20 days of the FDA's acceptance of a biosimilar application, the applicant provides the reference product sponsor—that is, the firm that makes the original biologic—with its full FDA application packet.[150] This packet includes the CMC section detailing its manufacturing methods in their entirety.

The BPCIA's information exchange is intended to facilitate the enforcement of the pioneer firm's patents on the biologic and its

148. Although a full CMC disclosure would generally allow for replication of the biologic for a follow-on entrant, in some cases deposition of the cell line might also be necessary.

149. 42 U.S.C. § 262(*l*) (2012). The mechanisms of this patent exchange are highly convoluted and not relevant to the purposes of this Article. For a detailed summary, see 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). Notably, the Federal Circuit has recently held that the patent-exchange provisions are not mandatory. Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1354–57 (Fed. Cir. 2015).

150. 42 U.S.C. § 262(*l*)(2).

manufacturing process. The information thus may be viewed only by the reference product sponsor's counsel, may not be disclosed to other employees, and may be used only to determine the possibility of patent infringement.[151] But the BPCIA provision also illustrates the extent to which the key codified information is found not in patents but in FDA regulatory submissions.

An FDA-centered approach poses some challenges, and a mandatory disclosure regime would be especially challenging. Most obviously, as a matter of political economy, it is unclear whether any powerful interest group would support mandatory disclosure. Insurance companies might have some interest, though they might be more interested in attempts to achieve public sector price regulation, on which they could then piggyback.[152]

More substantively, although certain claims about inadequate incentives as a consequence of mandatory disclosure might have questionable legitimacy, originator firms could legitimately point to the emerging global market for biologics in countries with limited patent enforcement and limited or nonexistent regulatory exclusivity regimes.[153] Mandatory disclosure could spur very swift competition within these countries. Biopharmaceutical firms rely heavily on arguments regarding global competitive impact in current debates over public release of clinical trial data submitted to the FDA.[154]

Additionally, mandatory disclosure that applied retroactively, to manufacturing method information already submitted to the FDA, might constitute a taking. In the 1984 case *Ruckelshaus v. Monsanto*, the Supreme Court held that Monsanto had established a property interest under Missouri trade secret law in the health, safety, and environmental information it had submitted to the EPA for purposes of obtaining regulatory approval.[155] Moreover, according to the Court, public release of data submitted prior to congressional enactment of a law placing Monsanto on notice that it should not expect data submissions to be confidential constituted a taking.[156] Lower

151. *Id.* § 262(*l*)(1)(B)–(D). Whether these requirements are readily enforceable is a matter of some debate, especially given the secrecy surrounding manufacturing operations normally.

152. As discussed in Part II, price regulation substantially misses the mark from the perspective of innovation.

153. COMM. ON STRATAGIES FOR RESPONSIBLE SHARING OF CLINICAL TRIAL DATA, *supra* note 123, app. C, at 260 (citing submissions from AbbVie and PhRMA arguing that China, Brazil, Australia, Chile, Mexico, Peru, Egypt, and Malaysia have limited regimes for regulatory exclusivity).

154. *See generally id.*

155. Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1003–04 (1984).

156. *Id.* at 1010–14. While we do not necessarily accept the view that mandatory disclosure would constitute a taking under *Ruckelshaus*—and indeed do not address the full contours of that argument here—its potential applicability nonetheless raises substantial legal and political economy challenges.

courts analyzing takings challenges to retroactive mandatory trade secrets disclosure have been similarly favorable to such challenges.[157]

Offering additional exclusivity as an incentive to biologics manufacturers to encourage voluntary disclosure would avoid takings concerns. The obvious objection is that firms would accept an additional regulatory exclusivity period only for those products where the period was longer than the likely market delay achieved by keeping manufacturing methods secret. Such gaming might be mitigated by requiring firms to opt in on a firm-wide rather than product-by-product basis. Moreover, for firms that are relatively risk-averse (for example, firms that have only one product), a guaranteed period of additional exclusivity, even if relatively short, could be superior to the risky exclusivity provided by trade secrecy.

Incentives could also take the form of accelerated FDA approval. As contrasted with exclusivity extensions, such acceleration might not only create less deadweight loss but might actually be more attractive to the originator. Given discount rates and technological advancement, reducing the time required for product development programs to reach the market and begin enjoying positive cash flow may be more important than additional regulatory exclusivity many years in the future.

The timing of disclosure also poses an interesting puzzle. In order to preserve originator incentives, particularly against the risk of very swift competition in countries without robust patent and regulatory exclusivities, disclosure should presumably not take place immediately upon originator approval. At the same time, disclosure occurring after patents and regulatory exclusivity expire would be too late to be useful for most follow-on firms.[158] The details of precisely when disclosure took place would therefore be very important.

Overall, disclosure administered through the FDA, most likely through some type of incentive scheme, has significant potential. Such disclosure would be helpful not only for purposes of producing competition but also as a rich source of information from which the larger scientific community could actively derive fundamental knowledge about manufacturing biologics.

Independent of whether such disclosure goes forward, however, nascent efforts by agencies like NIST to develop fundamental knowledge of biologic manufacturing processes and promote standardization of these processes should be encouraged. Quite appropriately, NIST's efforts attempt to leverage collective private sector knowledge. NIST thus draws upon a history

157. *See, e.g.*, Philip Morris Inc. v. Reilly, 312 F.3d 24 (1st Cir. 2002). Some have argued that retroactive application of the BPCIA pathway to originator manufacturers will inevitably constitute a taking because the FDA will have to compare the biosimilars' manufacturing process to that of the originator. *See generally* Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285 (2011). This latter argument has yet to achieve traction, however.

158. That said, even disclosure at a late date would contribute to the stock of knowledge.

of government-encouraged collaborative research and development among competitors. However, as we discuss below, while collaborative research and development efforts have generally involved competitors that are more or less similarly situated, the problem space in biologics manufacturing is more complex.

B. KNOWLEDGE GENERATION THROUGH COLLABORATIVE RESEARCH AND DEVELOPMENT

Understanding the challenges individual firms face in generating fundamental knowledge of biologics has led scholars and government actors to support not only public funding of such research but also in many cases private and public–private collaborative research and development.[159] As an empirical matter, however, collaboration between competitors is difficult, particularly in the biopharmaceutical industry. In this industry, studies of actual collaborative agreements reveal careful (and presumably laborious) allocation of future intellectual property rights to be an important part of contract design.[160]

In the biologics manufacturing context, the collaboration puzzle is even more complex. While most research and development collaborations involve firms that are roughly similarly situated, in this context players with relevant knowledge (or at least need for access to knowledge) include not only originator firms but also biosimilar firms. Given the disparity of competitive position, ex ante allocation of intellectual property rights seems unlikely. On the positive side, so long as sufficient ex ante incentives can be devised, the resulting knowledge will go into the public domain, with presumed additional spillover benefits.

Next, this Article gives some general background on the NIST Biomanufacturing Initiative. It then discusses three cases exemplifying different strategies on the part of firms and government actors. In the first case, improvements in fundamental knowledge appear to be perceived favorably by all parties, whether originator or biosimilar, FDA or NIST. In the second case, neither originator firms nor biosimilar firms are participating. In this case, originator firms may lack relevant knowledge, in part as a consequence of inflexible regulatory processes. Meanwhile, biosimilar firms may view the knowledge they have as a core competitive advantage. And in a

159. The National Cooperative Research Act of 1984 explicitly encourages such collaboration. *See generally* National Cooperative Research and Production Act of 1993, 15 U.S.C. §§ 4301–4306 (2012).

160. *See, e.g.*, Suzanne E. Majewski & Dean V. Williamson, *Incomplete Contracting and the Structure of R&D Joint Venture Contracts*, *in* 15 INTELLECTUAL PROPERTY AND ENTREPRENEURSHIP 201 (Gary D. Libecap ed., 2004). The Majewski and Williamson study relies on these government officials' ability to study contracts filed with the government under the National Cooperative Research Act of 1984, Pub. L. No. 98–462, 98 Stat. 1815 (1984) (prior to 1993 and 2004 amendments).

third category of cases, challenges may arise because of conflicts between agency actors.

1. The NIST Biomanufacturing Initiative

Since 2009, NIST has been working on a number of different fronts to develop fundamental knowledge about biologics manufacturing. Fundamental research in biologics manufacturing clearly fits within NIST's declared criteria for project priority setting: (1) "Magnitude/urgency of industrial need;" (2) "Correspondence between need and NIST mission to develop infrastructural technologies;" and (3) "Potential impact of NIST involvement."[161] The agency's overall title for the project—"Measurement Science and Standards to Support the Development of Novel Protein Therapeutics and Biosimilars"—reflects NIST's effort to appeal to both originator manufacturers and biosimilar manufacturers.[162] At least for purposes of initial engagement, NIST has succeeded. Its cadre of declared private and public sector partners includes all of the major biopharmaceutical and biosimilar manufacturers as well as the FDA.[163]

2. The NIST Cases

One basic challenge involves immunogenicity, particularly immunogenicity caused by aggregation.[164] Measurement can vary by a factor of ten, and measurement standards are needed.[165] To create measurement standards, 24 industry and academic participants have participated with NIST in a comprehensive measurement study.[166] A publication on this measurement issue has been submitted to the *Journal of Pharmaceutical Science*, and this information will soon be in the public domain.[167]

---

161. MICHAEL J. TARLOV, MEASUREMENT SCIENCE AND STANDARDS TO SUPPORT THE DEVELOPMENT OF NOVEL PROTEIN THERAPEUTICS AND BIOSIMILARS (2014), https://www.ibbr.umd.edu/sites/default/files/public_page/Tarlov%20-%20Biomanufacturing%20Summit.pdf.

162. *Id.*

163. According to the NIST website, industrial partners include "AbbVie, Agilent, Amgen, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Coriolis Pharmaceuticals, Eli Lilly, Genentech, GlaxoSmithKline, Human Genome Sciences-GSK, Janssen (Johnson & Johnson), MedImmune, Novartis, Novavax, PepsiCo, Pfizer, Roche, Sandoz, Thermo Scientific, [and] Waters." *Biomanufacturing Initiative*, NAT'L INST. STANDARDS & TECH., http://www.nist.gov/mml/bmd/biomanufacturing.cfm (last visited Jan. 10, 2016). Regulatory and standards partners include "the FDA, Health Canada, MPA-Sweden, NIBSC-UK, USP, [and] NIBRT-Ireland." *Id.* Academic partners include the "University of Birmingham, the University of Delaware, the Universities of Maryland (Baltimore and College Park) at the Institute for Bioscience and Biotechnology Research (IBBR), [and the] University of New Hampshire." *Id.*

164. Interview with Michael Tarlov, Head of Biomanufacturing, Nat'l Inst. of Standards & Tech. (July 1, 2014) (on file with authors); *see also* TARLOV, *supra* note 163.

165. TARLOV, *supra* note 163.

166. *See id.*

167. Interview with Michael Tarlov, *supra* note 166; *see also The Potential Need for Meaurement Standards to Facilitate the Research and Development of Biologic Drugs: Hearing Before the Subcomm. on*

Presumably originator and biosimilar firms do not perceive this area as one of core competitive advantage, whether the competition is other originator firms or biosimilar firms. To the contrary, at least if congressional testimony by Amgen on this question is representative, originator firms view immunogenicity as a very significant potential risk that they need to reduce but cannot cheaply reduce on their own.[168]

A second project on which NIST is working involves a collaboration with the FDA and Health Canada on a set of "best practices" for characterizing end-product biologics using NMR fingerprinting.[169] Although, as discussed in Part II, current public domain analytical methods for characterization are insufficient to show products are identical, these agencies are working to improve public domain information about characterization through NMR.

This project's efforts do not involve any industry participants. Notably, originator firms may not be interested in acquiring fundamental knowledge in this area of characterization for fear that the FDA will adopt a rule forcing the firms to use the technique post-approval but will balk if the results of the technique show even minor changes.[170] On the biosimilar side, a least one biosimilar firm, Sandoz, has used NMR, including for purposes of characterizing the biosimilar product it submitted for FDA approval in July 2014.[171] Sandoz may consider its knowledge a core competitive advantage.

In a third line of inquiry, NIST is spearheading the creation of a general-purpose standard monoclonal antibody for checking the performance of a variety of different analytical methods.[172] Although the results of this project will obviously assist in characterization, this indirect assistance is apparently not perceived as threatening core competitive advantage. To the contrary, 65 biopharmaceutical firm and academic participants are participating and the

---

Tech. & Innovation of the H. Comm. on Sci. & Tech., 111th Cong. 74–81 (2009) (testimony of Dr. Willie E. May, Director, Chemical Science and Technology Laboratory, National Institute of Standards and Technology).

168. *Id.* at 10–15 (statement of Anthony Mire-Sluis, Executive Director, Global Product Quality, Amgen Inc.).

169. Interview with Michael Tarlov, *supra* note 166; *see also* TARLOV, *supra* note 163.

170. *See* CTR. FOR BIOMEDICAL INNOVATION, SUMMARY: IMPLEMENTING INNOVATION IN BIOMANUFACTURING—THE HURDLES AND OPPORTUNITIES 3 (2011) (on file with authors) (noting that "despite . . . exciting advances in analytical capabilities it was unclear if pharmaceutical companies would take the risks necessary to adopt new technologies. On the one hand, new sensors will allow better process monitoring and control, enabling greater assurance that the product is the same for each batch. However, there is also a fear that if a company uses new methods to analyze its products it will see something it hasn't seen before. Such thinking has led some companies to never perform a new analytical test on an approved product. The question of whether to adopt new technologies was put most succinctly by a member of the regulatory science panel, 'What pain is going to be relieved? Which do I want more, relief of my pain or my money?'").

171. Hussain, *supra* note 63.

172. Interview with Michael Tarlov, *supra* note 166; *see also* TARLOV, *supra* note 163.

results will be featured in a forthcoming American Chemical Society book.[173] The material itself will be available through NIST at a nominal price.

NIST believes that both original and biosimilar firms will use the standard material in regulatory submissions.[174] Whether FDA should explicitly encourage use of the NIST standard poses an interesting question. Longstanding Executive Branch policy discourages government imposition of standards on private sector innovation.[175] But that position has been updated in the Obama Administration to emphasize:

> In limited policy areas . . . where a national priority has been identified in statute, regulation, or Administration policy, active engagement or a convening role by the Federal Government may be needed to accelerate standards development and implementation to help spur technological advances and broaden technology adoption. In these instances, the Federal Government can help catalyze advances, promote market-based innovation, and encourage more competitive market outcomes.[176]

The Obama Administration's Strategy for American Innovation specifically identifies national priorities with respect to health care technology and promoting clean energy.[177] To the extent that future administrations continue to see a more efficient health care system as a national priority, biologics manufacturing should be a prime area for achieving efficiencies. Consequently, the FDA's regulatory position may therefore be in tension not only with current Executive Branch policy but also future policy.

Part V turns to the general issue of the FDA's regulatory stance. Even if the NIST projects are unequivocally successful and NIST is then able to increase its current $10-million-a-year initiative, challenges remain.[178] Specifically, without appropriate flexibility on the part of regulatory authorities, fundamental understanding may prove useful for originator and

---

173. Interview with Michael Tarlov, *supra* note 166.

174. *Id.*

175. *See generally* OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, OMB CIRCULAR No. A–119—FEDERAL REGISTER (FEDERAL PARTICIPATION IN THE DEVELOPMENT AND USE OF VOLUNTARY CONSENSUS STANDARDS AND IN CONFORMITY ASSESSMENT ACTIVITIES), https://www.whitehouse.gov/omb/circulars_a119_a119fr.

176. Memorandum from Aneesh Chopra, U.S. Chief Tech. Officer, Office of Sci. & Tech. Policy, et al., to the Heads of Exec. Dep'ts & Agencies 2 (Jan. 17, 2012), https://www.whitehouse.gov/sites/default/files/omb/memoranda/2012/m-12-08.pdf.

177. *See generally* NAT'L ECON. COUNCIL & OFFICE OF SCI. & TECH. POLICY, A STRATEGY FOR AMERICAN INNOVATION (2015), https://www.whitehouse.gov/sites/default/files/strategy_for_american_innovation_october_2015.pdf.

178. By way of very rough comparison, SEMATECH, the prominent public–private consortium for improving semiconductor manufacturing processes, scaled up from an annual budget of $3 million in 1988 to $141 million in 1993 (figures not adjusted for inflation). *See* Albert N. Link et al., *Estimating the Benefits from Collaboration: The Case of SEMATECH*, 11 REV. INDUS. ORG. 737, 738 (1996).

biosimilar firms only up to the point of approval. In other words, if FDA continues to view approval as a "binary" event,[179] then the fruits of fundamental knowledge will be inadequately realized. In the next Part, we discuss this issue in the context of our broader discussion of adaptive regulation.

V. ADAPTIVE REGULATION

In recent years, some scholars who study regulation have argued that, in areas of rapidly evolving science and incomplete knowledge, regulation itself must be dynamic and adaptive.[180] Updating agency action has obvious costs. Even if the update, like the original agency action, is quite informal and thus does not have to go through elaborate administrative procedures such as notice-and-comment rulemaking, updates place significant information-gathering burdens on staff. Adaptive regulation may be particularly burdensome for agencies like the FDA that are asked to regulate a vast swath of the U.S. economy but are given only limited resources.[181] Moreover, changes in agency position may invite those who are hostile to the change to come up with creative legal challenge strategies. Although salient cases of inaction can sometimes be challenged,[182] action is on balance still easier to challenge than inaction. From the standpoint of industry, adaptive regulation also invokes the familiar trade-off between rules that may fit poorly but are stable and clear relative to flexible but uncertain standards.

That said, the social welfare losses associated with basing regulation on incomplete or outdated science are obvious. Moreover, in the area of drug approval, failure to regulate adaptively has an additional, subtler effect. If approval necessarily means that "drugs are generally perceived to be 'safe and effective'" upon licensure,[183] then the drug regulator is likely to require enormous amounts of data to approve the drug. Absent adaptive regulation, this problem is likely to become worse: Analysts increasingly recognize that current clinical trials are generally too small and too short to evaluate effects

179. *Cf.* H.-G. Eichler et al., *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 426, 427 (2012) (arguing "that knowledge of drugs is not binary but continues to evolve over time").

180. *See, e.g.*, Robin Kundis Craig & J.B. Ruhl, *Designing Adminstrative Law for Adaptive Management*, 67 VAND. L. REV. 1, 26 (2014). Some scholars who embrace adaptive regulation situate themselves in opposition with what they call "minimalist" approaches that stress cost-benefit analysis, efficiency, and market signals. *See, e.g.*, Charles F. Sabel & William H. Simon, *Minimalism and Experimentalism in the Administrative State*, 100 GEO. L.J. 53, 64 (2011) ("[T]he potential value of cost–benefit analysis is limited by its focus, at least in practice, on static factors as opposed to the capacity for learning and adaptation."). This Article does not engage in this debate.

181. *See, e.g.*, Peter Barton Hutt, Recent Developments, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 447–50 (2008) (discussing resource constraints at the FDA).

182. *See, e.g.*, Massachusetts v. Envtl. Prot. Agency, 549 U.S. 497, 505 (2007) (challenging the EPA refusal to regulate greenhouse gases).

183. *See* Eichler et al., *supra* note 181, at 426.

in the population as a whole.[184] The ultimate result may be requirements for ever-longer trials—presumably a result many stakeholders in biopharmaceutical development, ranging from firms to patients, would find dissatisfying.

Perhaps because of stakeholder pressure, proposals for one form of adaptive regulation—adaptive licensing wherein a drug could be approved for a small population and then subsequently have its use expanded to a larger population as more safety and efficacy data become available—have achieved some traction.

The EMA appears to be further ahead in this regard than the FDA.[185] In the United States, one concern has been the FDA's limited power to regulate physician decisions to prescribe drugs for unapproved populations or uses (so-called "off-label use").[186] Although the FDA Amendments Act of 2007 gives the agency somewhat greater power to impose risk-based restrictions, its authority to do so is cabined by federalism-infused concerns that states should maintain control over the practice of medicine.[187] That said, Massachusetts Institute of Technology political scientist Ken Oye, one of the principal proponents of adaptive regulation by the FDA, has worked with several lawyers (including Peter Barton Hutt, a former general counsel of the FDA) to identify a legal pathway for FDA expeditiously to approve a drug for a small population, with approval subsequently expanded to a larger population.[188] Others have suggested alternative adaptive approaches to regulate off-label use.[189]

Regulatory lock-in with respect to medicines is not limited to evaluation of clinical effectiveness. To the contrary, as discussed in Part II.C, for both small molecules and biologics, the FDA views the drug identity to be largely set at the time of approval; changes to the manufacturing process that impact drug characteristics are challenging, time-consuming, and expensive to justify, and other changes also face hurdles of time, expense, and uncertainty. Firms reinforce this regulatory resistance by tending to view the manufacturing process to be largely set at the time of approval.

This stasis is unjustified in the context of small molecules.[190] In the biologics context, FDA aversion to significant change post-approval is currently justified to the extent that fundamental knowledge is absent. But

184. *See supra* note 92.

185. *See, e.g.*, Hans-Georg Eichler et al., *The Risks of Risk Aversion in Drug Regulation*, 12 NATURE REVIEWS DRUG DISCOVERY 907 (2013).

186. *See generally* Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377 (2014).

187. *See generally id.*

188. K. Oye et al., *Legal Foundations of Adaptive Licensing*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 309, 310 (2013).

189. Abbott & Ayres, *supra* note 188, at 399–417.

190. *See* Price, *supra* note 73, at 519–22.

certain aspects of the FDA's very conservative approach may itself limit the development of fundamental knowledge. For example, as noted in Part IV.B, originator firms may be reluctant to develop more precise NMR fingerprinting tools out of fear that the FDA will mechanically demand very strict adherence to the more precise definition of the final product. Put another way, agency use of greater fundamental knowledge as a straitjacket itself discourages industry development of such knowledge.

Programs such as the NIST effort may soon produce greater fundamental knowledge.[191] At that point, FDA should no longer resist a more flexible approach. Indeed, in contrast to the area of physician prescribing practices post-approval, FDA unequivocally has the legal authority to allow post-approval manufacturing changes with significantly greater flexibility than the current bureaucratic process.[192]

FDA's recent guidance for biosimilar approval, discussed in Part II.D, does provide some grounds for optimism. This guidance explicitly adopts a stepwise approach wherein no single step is seen as a *sine qua non*. Although this guidance obviously applies only to the pre-approval stage, the principles it reflects could certainly be carried forward into the post-approval stage.

VI. CONCLUSION

Biologics increasingly dominate the front lines of medical innovation and are increasingly vital to doctors and patients. Drug companies pursue them in search of significant and ongoing profits. We have no problem with that pursuit: These ex ante incentives drive innovation in the biopharmaceutical industry. What is problematic, however, is the indeterminate restriction of information flow—and the resulting monopoly pricing—based not on the carefully crafted bargains of patent protection or regulatory restrictions, but on the interplay between secret information and the resulting specificity of FDA regulatory oversight. This interaction undermines the policy choice, made explicit in the BPCIA, that biologics, like small-molecule drugs, should have a limited period of exclusivity and then be opened up to competition. As a result, our healthcare system pays ever-increasing prices for biologics, and biosimilars seem unlikely to make much of a dent in those prices. Perhaps more insidiously, this pattern of indeterminate exclusivity relies on and perpetuates a lack of fundamental knowledge of the development and production of biologics. Firms face weak or nonexistent incentives to learn more about how biologics can be developed and produced, and may in fact face incentives to avoid developing such knowledge.

These challenges are not straightforward on either a scientific or a policy level, and point to the need for a more active innovation policy in the field of

191. *See supra* Part IV.

192. *See* 21 C.F.R. § 601.12 (2015) (discussing requirements for changes, including manufacturing changes, to an approved application).

biologics and biologics manufacturing. Government-sponsored initiatives such as those spearheaded by NIST are a step forward, but should be complemented by action to encourage and enable greater innovation by the private sector. In particular, the FDA can play a pivotal role, both by regulating adaptively to allow greater manufacturing innovation and by incentivizing disclosure of the codified information it already receives from biologics firms. With coordinated policy attention, the biologics sector can be driven toward greater innovation, greater transparency, and greater competition—an outcome that promises benefits for industry, healthcare cost containment, and, ultimately, patients.