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Using Data Exclusivity Grants to Incentivize Cumulative Innovation of Biologics' Manufacturing Processes

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Using Data Exclusivity Grants to Incentivize Cumulative Innovation of Biologics' Manufacturing Processes

Keywords

Patent, biologics, Pharmaceutical, drugs, Biologics Price, Competition, and Innovation Act, FDA, Biologics Price Competition and Innovation Act

COMMENTS

USING DATA EXCLUSIVITY GRANTS TO INCENTIVIZE CUMULATIVE INNOVATION OF BIOLOGICS' MANUFACTURING PROCESSES

ERIC LAWRENCE LEVI*

The pharmaceutical market is divided into two types of compounds: small-molecule chemical compounds and large-molecule biologics. Due to biologics' molecular sizes and the current scientific state of biologics manufacturing, manufacturing facilities and processes require frequent reassessment to ensure production of safe, pure, and potent therapeutics. Manufacturers utilize patent and drug regulatory law to protect their investments and simultaneously signal where innovation and investment are lacking. The current four- and twelve-year regimented structures of the Biologics Price, Competition, and Innovation Act do not keep pace with scientific development; biologics manufacturing processes drift with time, and if a manufacturer can obtain a higher degree of process control, then it should not feel restricted to wait until their exclusivity period lapses. Currently, the FDA rarely grants market exclusivity privileges for manufacturing process improvements alone; hence, manufacturing processes—or at least large portions thereof—are

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typically withheld as trade secrets or strategically claimed within companion composition claims. As a result, significant opportunity exists in regulatory framework to incentivize the research and development of biologics manufacturing processes. By creating a one- to four-year data exclusivity extension opportunity, manufacturers will feel more comfortable reinvesting their returns on investment towards manufacturing efficiency, and manufacturers can capitalize on the complex-molecule nature of their biologic.

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“We try to remember that medicine is for the patient. We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been.”

—George W. Merck¹

INTRODUCTION

Medical innovation continues to skyrocket, giving us artificial hearts, medical imaging software, advanced prosthetics controllable with the mind, and pharmacological cures for a plethora of dangerous diseases.² Notwithstanding our great strides to curtail certain genetic and biologic maladies, cancer and rare diseases in their various forms continue to proliferate.³ Legislators and regulators thus seek to incentivize this type of dramatic innovation while controlling patient costs and ensuring access to medicines.

This Comment attempts to explain and offer solutions for how patent and drug regulatory law address—or fail to address—commercialization and manufacturing inefficiencies when there are high barriers to biopharmaceutical product entry, particularly in the context of biologics. By working in tandem, patent law and drug regulations signal to the next generation of scientists, manufacturers,

1. MEDICINE IS FOR THE PATIENT, NOT FOR THE PROFITS 11 (1950).

2. For example, Crizotinib, a drug formed from living cells and carrying a price tag of \$50,000 per treatment, has been hailed as a miracle drug. It has singlehandedly eradicated certain subtypes of lung cancer once thought terminal in patients. AUSTL. DEP’T OF HEALTH, CRIZOTINIB, 200 MG CAPSULE, 60 AND 250 MG CAPSULE, 60, XALKORI®, PFIZER AUSTRALIA PTY LTD. 5 (Mar. 2014), <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-03/crizotinib-psd-03-2014.pdf>.

For a discussion of the potential revolutionary impact of a gene editing technique, CRISPR/Cas9, and how it is now being utilized in laboratories, see Yannis Grammatikakis, *Next Big Thing in Genome Modification: The CRISPR/Cas9 System*, NAT’L INSTS. HEALTH (Apr. 20, 2015), <https://irp.nih.gov/blog/post/2015/04/next-big-thing-in-genome-modification-the-crispr-cas9-system>; Thom Patterson, *Unproven Medical Technique Could Save Countless Lives, Billions of Dollars*, CNN (Oct. 30, 2015, 7:28 PM), <http://www.cnn.com/2015/10/30/health/pioneers-crispr-dna-genome-editing>.

3. Stacey Simon, *Cancer Statistics Report: Death Rate down 23% in 21 Years*, AM. CANCER SOC’Y (Jan. 7, 2016), <http://www.cancer.org/cancer/news/news/cancer-statistics-report-death-rate-down-23-percent-in-21-years>.

regulators, and business leaders where innovation and investment are lacking, encouraging smart innovation and investment. Designing biological products requires extensive investment and up-front development costs; similarly, biologics manufacturers require more process control compared to their small-molecule counterparts.

Therefore, so that manufacturers produce cheaper, safer, and more effective biologic and biosimilar cancer and rare-disease therapies (a.k.a. biobetters),⁴ Congress should provide greater incentive for manufacturing process innovation, disclosure, and societal health impact projections than those currently offered by the Biologics Price Competition and Innovation Act (BPCIA).⁵ Because small changes in biologics manufacturing processes require extensive comparability testing,⁶ manufacturers focus on comparing and mimicking biological products within tight preexisting constraints rather than developing and proving societal health benefits ancillary to manufacturing innovation.⁷ These alternative processes can result

4. See Mark McCamish & Gillian Woollett, *The State of the Art in the Development of Biosimilars*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 405, 405 (2012) (finding that altering earlier manufacturing processes empowers developers to evaluate prior biologics and commercialize a higher-quality and more cost-effective drug). Biobetters encourage manufacturing efficiency, new therapeutic uses, and lower consumer costs. *Competitive Strategies in Life Sciences: Biobetters Versus Biosimilars*, FINANCIER WORLDWIDE (Nov. 2011) [Hereinafter *Biobetters Versus Biosimilars*], <https://www.financierworldwide.com/competitive-strategies-in-life-sciences-biobetter-s-versus-biosimilars> (“[B]iobetter[s] will show improvement in one or more attributes over the original biologic, for example, in the form of a better side effect profile, faster action, lower dosing, or different form of delivery.”). These precision medications will simultaneously respond quicker to stimuli, minimize safety risks associated with immunological responses, and drive down production and consumer costs. See Helen Roe, *The Rise of Biosimilars in Cancer Care*, 24 BRITISH J. NURSING S28, S29 (Oncology Supp. 2015) (illustrating how biosimilars can be designed for different tumor groups, when previously there would have been only one drug for all).

5. Biologics Price Competition and Innovation Act (BPCIA) was enacted as part of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

6. U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., DRAFT GUIDANCE: COMPARABILITY PROTOCOLS FOR HUMAN DRUGS AND BIOLOGICS: CHEMISTRY, MANUFACTURING, AND CONTROLS INFORMATION 1, 3–4 (2016), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496611.pdf>.

7. Biologics and biosimilars—a regulated and discrete technology—have not developed into a statistically significant data set required to evaluate manufacturers’ specific focus, but “products of discrete technology industries [that] tend not to comprise integral components of some larger product or system . . . [and generally] do not enable the development of a wide array of ancillary products.” Robert P.

in anything from clinically tested child dosing regimens⁸ to brand-new therapeutic uses,⁹ illustrating how manufacturing processes can deliver return on investment (ROI) or fail to recoup costs. But innovators currently lack adequate incentives to develop and protect subsequent biologic manufacturing process improvements because the data and market exclusivity periods set forth in 42 U.S.C. § 262 are insufficient for an originator biologic manufacturer to (1) recoup its initial investment and (2) develop, test, and patent biobetter processes. By examining and correcting these deficiencies, and by offering a more flexible regulatory scheme rather than a one-size-fits-all paradigm, the signaling and notice functions inherent in patent and drug regulatory law will guide the next generation of innovators and corporations toward smarter investing in the biologics manufacturing improvements that best improve societal health.

Biologics manufacturing processes create unique opportunities for sponsors and manufacturers to leverage existing patent rights and obtain justified exclusivity while enhancing societal health. To best allow manufacturers to take advantage of these opportunities, legislative corrections must be made whereby the governmental grant of exclusivity built into the BPCIA would require showing projected societal health impact. Additionally, the societal impact should correspond with a tiered market exclusivity system such that manufacturers maintain the incentive to conduct further research and development (R&D) on existing rights while pursuing opportune protection of any supplemental high-quality innovation. The recent

Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 880–81 (1990).

8. 42 U.S.C. § 262(m) provides a pathway for approval of child dosing regimens, but manufacturers should have the incentive to pursue these regimens on their own accord while attempting to enhance manufacturability, thereby lowering risk financial risk with multiple facets of potential protection and exclusivity. See W. Nicholson Price II, *Innovation Policy Failures in the Manufacturing of Drugs*, in FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 354–55 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015) [hereinafter Price, *Innovation Policy Failures*] (arguing that the FDA’s role in encouraging pediatric studies could also be used to encourage innovative manufacturing methodology).

9. See *Biobetters Versus Biosimilars*, *supra* note 4 (“Depending on the process to create biobetters, the platform may also be applicable to more than one product, thus saving substantial development dollars,” as was the case for Aranesp, launched prior to the expiration of original patents covering EPO).

decision in *Amgen Inc. v. Apotex Inc.*¹⁰ and the pending litigation of *AbbVie Inc. v. Amgen Inc.*¹¹ illustrate the serious concern reference product sponsors (“RPS”) have for obtaining and maintaining market exclusivity—these barriers for follow-on biologics (“FOB”) manufacturers must be predictable and valuable whenever an applicant seeks market and data exclusivity. The inherent value of biologics manufacturing processes will either be disclosed for public knowledge or concealed as a trade secret, exemplifying the trade-offs in the patent-or-trade-secret dichotomy.¹² Increased disclosure of firms’ biologics manufacturing processes—both by biosimilar and RPS applicants—will enhance biological agent efficacy, purity, and safety across the industry. Furthermore, as scientific understanding of biologics moves “from [a] reductionistic understanding of biochemical pathways to organism-level models[, a bridge will be built] between current empirical methods of drug candidate evaluation and new models of drug development.”¹³ Therapeutic treatments are impacted by both the unique characteristics of biologics manufacturing processes and recent judicial decisions, illustrating that biopharmaceuticals should be the most innovative and scientifically current methodology for personal and precise therapeutic care.¹⁴

By rewarding manufacturers for their enhanced process knowledge with a tiered data exclusivity system,¹⁵ manufacturers will re-invest in drug quality, efficacy, and safety improvements while passing on lower costs to consumers.¹⁶ The shorter yet predictable FDA data exclusivity grants are best capable of incentivizing biologics manufacturers to innovate and disclose improved manufacturing methodology because of the constant refinement and reassessment inherent in biologics manufacturing. In the rare disease market, where competition is often sparse, innovators require additional

10. 827 F.3d 1052 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 591 (2016) (holding FOB sponsors must provide 180-day notice of commercial marketing to the RPS, after approval of their FOB but prior to marketing the FOB).

11. Complaint, *AbbVie Inc. v. Amgen Inc.*, No. 16-666-SLR (D. Del. Aug. 4, 2016).

12. See *infra* Part IV.

13. J. Woodcock, “Precision” Drug Development?, 99 CLINICAL PHARMACOLOGY & THERAPEUTICS 152, 153 (2016).

14. See *Innovation Saves*, BIOTECHNOLOGY INNOVATION ORG., <http://innovationsaves.life> (last visited Feb. 5, 2017) (describing how innovation in biologics saves lives and money).

15. Price, *Innovation Policy Failures*, *supra* note 8, at 343, 354–55 (correlating manufacturing design changes with innovative value).

16. Woodcock, *supra* note 13, at 153.

incentive to improve their manufacturing processes because there is less fear of competitor FOB manufacturers utilizing a more efficient or efficacious manufacturing process.¹⁷ For biologics and biosimilars to capture market share quicker, customers and clinicians must view the incremental advantages of biologics over small-molecules as worthwhile given the price difference; therefore, innovator biologics manufacturers should have the first opportunity—before the conclusion of market exclusivity—to provide scientific data supporting the therapeutic value of their medications compared to any small- or large-molecule drugs.

This would advance BPCIA's two-fold mission: (1) providing sufficient incentives for continuous innovation in biologic therapies (i.e., promoting innovation) and (2) lowering the price of biologic therapies (i.e., promoting accessibility),¹⁸ as well as the Constitutional goal of “promot[ing] the Progress of Science and useful Arts” for societal benefit.¹⁹ Innovative value and public accessibility go hand-in-hand when determining price. Because biologics manufacturers possess first-hand biologics-process-based scientific knowledge of safety, efficacy, and potency, they can project societal health improvements relatively accurately.

Similarly, the value of biopharmaceutical therapeutics change as scientific knowledge develops. Justifying exorbitant prices for a single pharmaceutical becomes harder as generics and FOBs respond to market demands and statutory exclusivities or patent grants expire. Thus, recurring opportunities for biologics manufacturers to leverage previous grants and obtain an additional FDA grant of data exclusivity or PTO patent grant will lower biologics prices; even though exclusivity lends itself to short-term price hikes, greater flexibility enables greater efficiency as grants enable drug prices to closely track the actual need and demand of the drug.²⁰ Lower prices will make

17. Carefully calibrated data exclusivity periods can identify and reward socially beneficial investment. Sarah Sorscher, Note, *A Longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy*, 23 HARV. J.L. & TECH. 285, 302 (2009). Furthermore, sponsors can pursue patent grants to target areas not covered by data exclusivity. Vincent J. Roth, *Will FDA Data Exclusivity Make Biologic Patents Passé?*, 29 SANTA CLARA COMPUTER & HIGH TECH. L.J. 249, 249 (2013).

18. Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, § 7001(b), 124 Stat. 119, 804 (2010) (“It is the sense of the Senate that a biosimilars pathway balancing innovations and consumer interests [i.e., accessibility] should be established.”).

19. U.S. CONST. art. I, § 8, cl. 8.

20. Enabling more “smaller steps” in exclusivity grants achieves the lowest possible price in the long run, as opposed to twelve-year leaps, which will keep

the market accessible to more customers while incentivizing high-quality innovation that more accurately reflects market forces and needs rather than arbitrary legislative grants, allowing the new biological products marketplace to adapt and keep pace alongside scientific advancements in biologics manufacturing processes.

Part I of this Comment illustrates how biological products capture market share and sets up how drug regulatory law may be used as a lever to adjust incentives to promote disclosure of biologics manufacturing processes. Part II examines FDA requirements for grants of exclusivity and how biosimilars subsequently gain market approval. Part III analyzes the trade-offs between patents and trade secrets under 35 U.S.C. § 112's claim scope disclosure requirements. Part IV applies property law to the biologics and biosimilars abbreviated pathway framework to assess current manufacturing process protection risks and opportunities. Subsequently, Congress should create a tiered data exclusivity system because biologic-specific FDA grants of data exclusivity and early investments in improving patented processes enhance drug quality and more accurately reflect the realities of a complex and ever-changing scientific and financial landscape.

I. THE INCREASING BIOLOGICAL PRODUCT MARKET SHARE

Eliminating cancer cell-by-cell may seem like an impossible task, but what if an army of tiny, “incredibly sophisticated killing machines”²¹ are grown to bear the brunt of that work? Indeed,

overall biopharma prices higher, long-term. The assumptions inherent in exclusivity indirectly curing high price include: (1) the innovator discloses sufficient information to incentivize high quality follow-on biologics manufacturing processes, (2) the innovator has an incentive to adapt and perfect their current biologics manufacturing processes, and (3) biologics (and the exclusivities which facilitate novel medicine market growth) in the long run will be cheaper for consumers than their small molecules. Thus, getting the most societally beneficial biologics approved and into the market quicker in order to pave the way for biosimilars and other new biologics, will lead to lower health-care costs.

With greater flexibility comes great efficiency—i.e., grants are proportional to the innovation. In some cases, it may lead to higher drug prices when warranted, but for the most part it will more closely track the actual need and demand of the drug, while conforming to a less artificial, one-size-fits-all regulatory model. Twelve to twelve-and-a-half years makes little sense for some incremental advancement; but for a major advancement, it could be paramount.

21. *On Assignment: Hacking Cancer*, NBC NEWS (May 20, 2016, 8:14 AM), <http://www.nbcnews.com/widget/video-embed/690231363507> (quote appears at 3:35 in video).

biopharmaceuticals—or biologics²²—allow clinicians to create personalized and precise therapeutic plans of attack for cancer and cancer-causing agents. “The importance of biologics lies in their structural and functional variety,” enabling clinicians and pharmacists to treat diseases not effectively treated with small-molecule drugs.²³ But sophistication and complexity come with a high price tag, increased health risks, and more stringent regulatory standards. These barriers to innovation and biopharmaceutical market entry are balanced with Patent and Trademark Office (PTO) grants of patent rights as well as two types of Food and Drug Administration (FDA) grants of valuable innovator exclusivity—a statutory grant of market and data exclusivity through the BPCIA.²⁴ Traditional patent exclusivities prevent FOB manufacturers from using, selling, or importing the patented biologic²⁵—effectively granting the right to exclude others from the market by suing for huge damages awards—while data exclusivities prevent FOB manufacturers from using the RPS’s clinical trial data when submitting an abbreviated biologics license application (aBLA) and market exclusivities preclude the FDA from approving an aBLA. Essentially, data exclusivity inhibits the development of FOB manufacturing processes and market exclusivity prevents the FDA from approving an FOB, prolonging FOB market entry.

Most biologics manufacturers will take advantage of redundancies in exclusivity grants. Because manufacturers pursue safe, efficacious, and pure biologics to gain approval by the FDA, they often develop

22. Kate S. Gaudry, *Exclusivity Strategies and Opportunities in View of the Biologics Price Competition and Innovation Act*, 66 FOOD & DRUG L.J. 587, 587 (2011) (explaining that biological products, biologics, or “[b]iologics are a class of drugs or vaccines that are produced by manipulating a living tissue or microorganism”).

23. Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 422 n.4 (2012).

24. 42 U.S.C. § 262(k)(7) (2012). For an in-depth look at the legislative history outlining developments of the biologics and biosimilars pathway, illustrating bargaining between generics, innovators, and the FDA, see generally Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

25. 35 U.S.C. §§ 101, 271(a) (2012). These patent exclusivities can be worth billions of dollars. See, e.g., Christopher Yasiejko & Susan Decker, *Merck Wins Record \$2.5 Billion Patent Verdict Against Gilead*, BLOOMBERG (Dec. 15, 2016, 4:30 PM), <https://www.bloomberg.com/news/articles/2016-12-15/gilead-told-to-pay-merck-2-54-billion-in-hepatitis-c-royalties> (reporting that a jury awarded Merck & Co. \$2.5 billion, which is the equivalent of ten percent royalties, based on Gilead Science’s use of its patented drug compound to treat hepatitis C).

biological compounds in conjunction with manufacturing processes that are ripe for patenting. Thus, innovators can earn statutory exclusivity for biologics testing data for twelve to twelve and a half years as well as patent portfolio rights (i.e., active patent life) for the biological compound and/or manufacturing process coextensively, where patent protection may extend five to eleven months longer.²⁶ Still, with biologics development times generally running longer than those of traditional single-molecule drugs, the data exclusivity will oftentimes exceed patent exclusivity for the innovative new chemical entity or process of which the manufacturer received patent protection.

To advance biologics manufacturing processes at a rate consistent with rapid scientific development, legislation must encourage biologics manufacturers, in the form of biologics licenses and patent rights, to pursue regulatory approval more often. These more frequent *quid pro quo* disclosure opportunities—supported by showing improvement to societal health—should change current regime trends: innovator biologics companies should disclose scientific knowledge about their biologics manufacturing processes more frequently than once at the beginning of their twelve-year market exclusivity period or (generally) twenty-year patent grant unless the societal health improvement is so substantial that a four-year data exclusivity and twelve-year market exclusivity period is justified. As biologic originators' exclusivity periods expire, biosimilars (and in the future, interchangeable) manufacturers similarly disclose bare minimum manufacturing process knowledge, as they rely on safety and effectiveness clinical-trial data from the RPS.²⁷ By legislatively creating a tiered data exclusivity system within 42 U.S.C. § 262(k)(7)(B), whereby the Secretary accepts an additional data exclusivity application from the originator prior to the expiration of their previously granted data exclusivity period, biologic manufacturing process knowledge will grow alongside scientific development; for both the original data exclusivity grant and

26. 42 U.S.C. § 262(k)(7); Heled, *supra* note 23, at 423–24. Professor Yaniv Heled provides a compelling case study and graphical depiction, illustrating when initial research and development on a biologics begins, demonstrating how typical patent terms and exclusivity periods overlap. *Id.* at 449.

27. 42 U.S.C. § 262(k)(2) (detailing the requirements to apply for licensure of biological products as a biosimilar); Gaudry, *supra* note 22, at 587, 592. Compare 42 U.S.C. § 262(k)(2) (relying on safety and effectiveness data for large-molecule biopharmaceutical drugs), with 21 U.S.C. § 355(j) (relying on safety and effectiveness data for small-molecule chemical drugs).

subsequent data exclusivity application, the Secretary will determine—on a case-by-case basis—the appropriate one- to four-year data exclusivity period. Ideally, the inefficiencies that plague small-molecule originator and generics manufacturers will be minimized in the biologics and FOB manufacturing environment as more information is released in stages.

Disclosing scientific advances has obvious pros and cons,²⁸ but the ultimate question is whether the innovator feels he can obtain an ROI by capturing market share to set up prospective growth.²⁹ When comparing a brand-name or generic small-molecule applicant with a biologics or biosimilar applicant, respectively, given the high rate of failure, there must be a significantly larger ROI than the “300 billion [dollars that was spent] on research and development (R&D) with such little improvement over the last twenty years in the life expectancy of patients.”³⁰ Currently, biopharma has the highest rate of reinvestment in R&D of any U.S. industry—approximately nineteen percent.³¹ If product sponsors and manufacturers lower or reallocate

28. Manufacturing process transparency will allow firms to easily police manufacturing patents, which would in turn provide greater incentives to innovate. Price, *Innovation Policy Failures*, *supra* note 8, at 343, 354.

29. Potentially creating independent pathways to validate new technologies outside of the new drug application (NDA) and BLA process or creating new disclosure opportunities for biologics manufacturers would provide ROI viability options. *Id.* at 353 (suggesting that establishing a market for innovative drug manufacturing technologies would provide additional disclosure incentives and economically enticing licensing schemes).

30. *On Assignment: Hacking Cancer*, *supra* note 21 (quote appears at 7:39 in video); see also Els Torreele, *Should Patents on Pharmaceuticals Be Extended to Encourage Innovation?*, WALL ST. J. (Jan. 23, 2012), <http://www.wsj.com/articles/SB10001424052970204542404577156993191655000> (showing that patent duration and scope have increased, and research-and-development spending has increased yet “new molecular entitles” have decreased forty-five percent since the late 1990s).

31. JANSSEN PHARMACEUTICA, HIGH VALUE, HIGH UNCERTAINTY: MEASURING RISK IN BIOPHARMACEUTICAL RESEARCH AND OTHER INDUSTRIES 12 (2014) <https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences/Health-Care/gx-lshc-measuring-risk-in-biopharmaceutical-research.pdf>; see also PHARM. RESEARCH & MFRS. OF AM., 2015 PROFILE: BIOPHARMACEUTICAL RESEARCH INDUSTRY 25 (2015), http://phrma-docs.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf (explaining that biopharma invests “more than 13 times the amount of R&D per employee than manufacturing industries overall”); Michael Casey & Robert Hackett, *The 10 Biggest R&D Spenders Worldwide*, FORTUNE (Nov. 18, 2014, 8:45 AM), <http://fortune.com/2014/11/17/top-10-research-development> (illustrating that two industries—health care and computers—account for half of all R&D investment); *Innovation Saves*, *supra* note 14 (describing the results of such heavy investment in R&D).

reinvestments toward R&D, inefficiencies will continue to plague the biopharmaceutical manufacturing process. High-quality innovation, on the other hand, utilizes an originator's scientific expertise to focus investments on manufacturing "drift" and inefficiency to ultimately create a more valuable consumer product. Biologics manufacturing processes and their associated analytical tools are the backbone of innovation in the biological products market. Because precision medications and rare disease treatments require high initial investment and occasionally expensive companion genetic testing, neither being properly incentivized within the BPCIA, the biological products landscape is poised for change.

A. *Defining Biological Products*

Biological products³² are at the forefront of biomedical research and are complex mixtures not easily identified or characterized.³³ The FDA defines biological drugs as agents containing over forty amino acids manufactured *in vivo*—typically through recombinant DNA technology.³⁴ Therefore, biologics are isolated from natural sources.³⁵ In time, biologics—coming from living precursors—may offer the most effective means to treat complex medical illnesses and conditions.³⁶ Their curative media include gene therapy, regenerative medicine, enzyme replacement,³⁷ immune-oncology, precision medicine,

32. A biological product is defined as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1).

33. W. Nicholson Price II, *Regulating Secrecy*, 91 Wash. L. Rev. 1769, 1769 (2016) [hereinafter Price, *Regulating Secrecy*] ("Biologics, which comprise the most innovate and expensive drugs today, are the path-dependent result of complex, secret manufacturing processes.").

34. Lynne A. Bui et al., *Key Considerations in the Preclinical Development of Biosimilars*, DRUG DISCOVERY TODAY SUPPLEMENT, May 2015, at 3, 4.

35. Biologics "are produced and purified from living systems such as bacteria, yeast or mammalian cell lines." *Id.* at 3.

36. Bradford R. Hirsch & Gary H. Lyman, *Biosimilars: A Cure to the U.S. Health Care Cost Conundrum?*, 28 BLOOD REVIEWS 263, 263 (2014); see also V. Strand & B. Cronstein, *Biosimilars: How Similar?*, 44 INTERNAL MEDICINE J. 218, 218 (2014) (stating that monoclonal antibodies, soluble receptors, cell surface antigens, and co-stimulation signals represent the "most complicated" of biologic agents).

37. The most common manner for production of therapeutic proteins is generally recombinant proteins produced by host cells. Florian M. Wurm, *Production of Recombinant Protein Therapeutics in Cultivated Mammalian Cells*, 22 NATURE BIOTECHNOLOGY 1393 (2004), <http://www.nature.com/nbt/journal/v22/n11/full/>

vaccines, and other agents critical for maintenance of disease states including cancer and autoimmune diseases.³⁸

Because biologics are made from living organisms, the functional-, safety-, and efficacy-related properties of a biologic depend heavily on their manufacturing and processing conditions.³⁹ A difference of one degree in manufacturing can lead to denatured proteins and ineffective treatments. While biologics can harness the therapeutically useful aspects of naturally-occurring cellular responses, their manufacturability and batch-to-batch drift require a more complex and supervised examination. This process is incredibly sensitive; small changes in extra-cellular matrix pressure, temperature, solubility, etc. undoubtedly affect cellular communications, rendering a biologic useless (and potentially dangerous) or efficacious.⁴⁰

While manufacturing processes attempt to mimic *in vivo* extra-cellular matrices, product variability with each subsequent batch is inevitable. Difficulties in classifying the proteins within a biologic and non-precise manufacturing processes mean that clinical assessments must approve of a process based on its precision⁴¹ rather than its accuracy.⁴²

nbt1026.html.

38. *Innovation Saves*, *supra* note 14; see also Charles L Bennet et al., *Regulatory and Clinical Considerations for Biosimilar Oncology Drugs*, 15 LANCET ONCOLOGY 594, 594 (2014); Farah Huzair & Dinar Kale, *Biosimilars and the Long Game*, 33 TRENDS IN BIOTECHNOLOGY 250, 250 (2015); Merges & Nelson, *supra* note 7, at 905; Adam Ross & Kelly Richard, *Biosimilars*, 79 CONN. MED. 295, 295 (2015).

39. Bui et al., *supra* note 34, at 4 (“[B]iologics are proteins that are typically much larger than chemically synthesized small-molecule drugs, exhibit a high degree of structural complexity, including primary, secondary, tertiary and possibly quaternary structures, and are subject to post-translational modifications.”); see also Darren S. Tucker & Gregory F. Wells, *Emerging Competition Issues Involving Follow-on Biologics*, ANTITRUST, Fall 2014, at 100, 100 (noting that changing the manufacturing process could modify the product in ways that might not be detected, yet may alter safety or efficacy). For an overview of the small-molecule drug versus large-molecule biologic divide, and how their characteristics and manufacturing conditions are inherently considered and contrasted in both the BPCIA and Hatch-Waxman Act, see generally Trevor Woodage, *Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-on Biologics and Barriers to Their Approval and Commercialization*, 2012 STAN. TECH. L. REV. 9.

40. Bennet et al., *supra* note 38, at 599 (stating that changing immunogenicity profiles can be due to cell lines or media components, structural modifications, protein aggregation, suboptimum storage processes, and patient factors).

41. Precision refers to the closeness of two or more measurements to each other. Precision medicine and precision drug manufacturing go hand-in-hand. “We are entering an era of precision medicine, when drugs must be made with unique

Originator biologics and biosimilar pharmaceuticals will inevitably gain market share. However, if manufacturers continue to use the same manufacturing process for up to twelve and a half years of market exclusivity or twenty years from filing a patent application, the same drug shortage, recall, and overall inefficiency issues that plague the small-molecule pharmaceutical industry will consume the growing biopharmaceutical industry.⁴³

B. Biosimilars' Movement into the Market Place

“Biosimilar”⁴⁴ is a term used to describe an FOB drug whose target is the same as that of the originator biologic, similar to the relationship between generics and brand name pharmaceuticals.⁴⁵ Biosimilars are functional equivalents of an originator biologic and require less clinical trial data for approval.⁴⁶ As biologics' patents and exclusivity grants expire, biosimilar manufacturers have the opportunity to claim alternative or more efficient methods of manufacture.

features” that are replicable by continuous manufacturing. Lawrence Yu, *Continuous Manufacturing Has a Strong Impact on Drug Quality*, U.S. FOOD & DRUG ADMIN.: FDA VOICE (Apr. 12, 2016) <http://blogs.fda.gov/fdavoices/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality>.

42. Bui et al., *supra* note 34, at 3 (listing biosimilar development steps: (1) “selection of an appropriate reference biologic,” (2) “understanding the key molecular attributes of that reference biologic,” and (3) “development of a manufacturing process to match these attributes of the reference biologic product”); *see also* W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars?*, 348 SCI. 188, 188 (2015). Accuracy measures how close a result (or process) tracks with the true, pre-determined value. Accuracy ensures the repeatability of process parameters—and therefore products—in biologics manufacturing. Jim Cahill, *Accurate and Repeatable Measurements in Pharmaceutical and Biotech Manufacturing*, EMERSON PROCESS MGMT. (Mar. 15, 2016), <https://www.emersonprocessxperts.com/2016/03/accurate-and-repeatable-measurements-in-pharmaceutical-and-biotech-manufacturing>.

43. For a complete list of FDA inspection citations, see *Inspections Citations*, U.S. FOOD & DRUG ADMIN. (Sept. 2, 2016), <http://www.fda.gov/ICECI/Inspections/ucm346077.htm>.

44. *See* McCamish & Woollett, *supra* note 4, at 409 (explaining that changing manufacturing processes, whether by scaling or by creating a biosimilar, will slightly modify the structure and function of the resulting biomolecules, which is why these products are referred to as “biosimilar,” rather than “biogeneric” or “bioidentical”).

45. *Id.* at 405 (noting that biosimilars must meet strict requirements of quality and comparability to the originator biologic).

46. *See Information for Industry (Biosimilars)*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm> (last updated Jan. 12, 2017).

Currently, the hallmark of the biologics market is high price.⁴⁷ Biologics routinely cost consumers between \$50,000 and \$250,000 for a single year of treatment.⁴⁸ But as biological products come off-patent and their exclusivity periods expire, biosimilars will naturally capture market share⁴⁹ without the systemic patent-cliff issues⁵⁰ posed by the small-molecule generics market.⁵¹ Instead, the high cost of manufacturing and ensuring quality control will limit generic involvement regardless of patent protection, diminishing immediate competition and creating market-driven barriers on entry. Subsequent competition reinforces manufacturing efficiency and minimizes new investors' risk. Drugs represented ten to fourteen percent of American health-care costs in 2015,⁵² and increased competition threatened by and due to the biosimilars market offers customer savings of at least eight to ten billion dollars a year.⁵³

47. Bennet et al., *supra* note 38, at 594 (“In 2016, half of the ten most expensive pharmaceuticals will be biologicals.”).

48. Tucker & Wells, *supra* note 39, at 100; *see infra* text accompanying note 76 (noting that biologics may cost greater than twenty times more than a small-molecule drug).

49. *See* G. Dranitsaris et al., *Clinical Trial Design in Biosimilar Drug Development*, 31 INVESTIGATIONAL NEW DRUGS 479, 480–81 (2013) (noting that by 2017, \$60 billion worth of brand biologics will be coming off patent protection in developed countries); Roe, *supra* note 4, at S28 (suggesting that biosimilars are safe and effective alternatives particularly because of the regulatory stringency around development, manufacturing, and licensing); *see also* Strand & Cronstein, *supra* note 36, at 218–19 (discussing the interest in producing biosimilars to counteract the “significant financial burden” of biologic therapies, which often limits their use to patients in wealthier countries).

50. Patent cliff issues refer to the fact that there are less small-molecule blockbuster drugs capable of being discovered, and as these drugs lose patent protection, market prices and incentives to innovate will drastically change. *See generally* Chie Hoon Song & Jeung-Whan Han, *Patent Cliff and Strategic Switch: Exploring Strategic Design Possibilities in the Pharmaceutical Industry*, 5 SPRINGERPLUS 692 (2016).

51. Erwin A Blackstone & Joseph P. Fuhr Jr., *Biologics & Biosimilars: The Possibility of Encouraging Innovation and Competition*, SCITECH LAW., Spring 2015, at 4, 5–6; Huzair & Kale, *supra* note 38, at 252.

52. *Affordable*, BIOTECHNOLOGY INNOVATION ORG., <http://innovationsaves.life/affordable> (last visited Feb. 5, 2017).

53. Gaudry, *supra* note 22, at 589. “We predict that biosimilars will lead to a \$44.2 billion reduction in direct spending on biologic drugs from 2014 to 2024, or about 4 percent of total biologic spending over the same period, with a range of \$13 billion to \$66 billion.” ANDREW W. MULCAHY ET AL., RAND CORP., THE COST SAVINGS POTENTIAL OF BIOSIMILAR DRUGS IN THE UNITED STATES 1 (2014), https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf.

Besides having similar molecular shape, efficacy, and safety to biologics,⁵⁴ biosimilars will by nature provide lower cost-alternatives. Lower regulatory and financial barriers offer biologics manufacturers with more incentives to disclose manufacturing information in return for patent protection and exclusivity rights. The biosimilar market discount versus the cost of originator biologics will be between twenty and forty percent for consumers, while historically the small-molecule generics market discount was around eighty percent in comparison to brand-name small-molecule pharmaceuticals.⁵⁵ Because the market for oncology biologicals alone is over \$100 billion, the innovation of originator biologics and biosimilars provide significant opportunity to pass savings on to consumers.⁵⁶

C. Inherent Scientific Development Differences Between Small-Molecule and Large-Molecule Pharmaceutical Compounds

Research and development of biological therapies proliferated in response to inefficiencies in production and therapeutic precision within the small-molecule generics market.⁵⁷ Generics make up over eighty percent of filled prescriptions in the United States, illustrating market saturation and a fast eroding market for small-molecule

54. Bennet et al., *supra* note 38, at 594.

55. *Id.* at 596; Hirsch & Lyman, *supra* note 36, at 264, 267; Steven D. Lucio et al., *Biosimilars: Implications for Health-System Pharmacists*, 70 AM. J. HEALTH-SYS. PHARMACY 2004, 2008, 2011–12 (2013).

56. Bennet et al., *supra* note 38, at 594; Price, *Innovation Policy Failures*, *supra* note 8, at 344 (emphasizing that reducing excessive manufacturing costs could generate tens or hundreds of billions of dollars in consumer savings). Manufacturing costs are either the first or second highest expense for sponsor drug firms. *Id.* “The successful integration and uptake of biosimilars in oncology may help to expand choices for clinicians and patients and increase accessibility to potentially beneficial treatments.” Katherine H. Rak Tkaczuk & Ira Allen Jacobs, *Biosimilars in Oncology: From Development to Clinical Practice*, 41 SEMINARS ONCOLOGY 3, 11 (2014) (reporting that a study of 118 community-based oncologists found that nearly sixty percent now consider drug costs in clinical decision making, “roughly half reported the need to change treatment plans due to the loss of medical insurance, and 58% reported that patients refused treatment due to the financial concerns”).

57. See Dranitsaris et al., *supra* note 49, at 479 (describing the shift toward the development of biologics during the past two decades); Edward C. Li et al., *Considerations in the Early Development of Biosimilar Products*, DRUG DISCOVERY TODAY, May 2015, at 1 (noting that as the biologics market grows, changes in pharmaceutical product development will lead to more biosimilars as well).

drugs.⁵⁸ In contrast to large molecule biosimilars, current regulation requires that small-molecule generics be the “bioequivalent” of its corresponding brand drug.⁵⁹ A bioequivalence standard, requiring a well-controlled and “well-defined chemical structure and physiochemical properties,”⁶⁰ illustrates the scientific community’s acceptance of easily classifying and replicating small-molecule reactions. These manufacturing processes are relatively easy to replicate and set consistent standards for a quality product.⁶¹

On the other hand, biologics have much larger molecular sizes and structures,⁶² consequently creating more uncertainty and difficulty in product standardization.⁶³ Critical to safety and efficacy of biosimilars are studies of stability, pharmacokinetics, and

58. See Peter Wehrwein, *A Conversation with Steve Miller, MD: Come in and Talk with Us, Pharma*, MANAGED CARE (Apr. 2015), <http://www.managedcaremag.com/linkout/2015/4/27> (discussing how, by spurring innovation and lowering costs, pharmacy benefit managers, such as ExpressScripts, influence market saturation and consumer demand by acting as a medium that balances market disruption with savings, thereby analyzing data and sifting through the biopharmaceutical market to determine where consumer money is best spent); see also Simon King, *The Best Selling Drugs of All Time; Humira Joins the Elite*, FORBES (Jan. 28, 2013, 9:58 AM), <http://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite> (illustrating biologic Humira’s ability to capture market share).

59. 21 C.F.R. § 320.33 (2016).

60. Preeta Kaur Chugh & Vandana Roy, *Biosimilars: Current Scientific and Regulatory Considerations*, 9 CURRENT CLINICAL PHARMACOLOGY 53, 56 (2014).

61. *Id.* at 53; see also Thomas Reinke, *Encouraging Guidance Released for Biosimilar Manufacturers*, MANAGED CARE (Aug. 2014), <http://www.managedcaremag.com/linkout/2014/8/10> (stating that meeting well-defined bioequivalence or interchangeable status implies greater market acceptance).

62. Dranitsaris et al., *supra* note 49, at 479 (“[B]iological drugs are derived from living organisms or their products. Biologicals are structurally more complex and unique from chemically synthesized [small-molecule drugs] because of their larger size and intricate manufacturing process. Secondary to their protein structure, they are also more prone to acute and chronic immune responses.”). Typically, biologicals are one hundred to one thousand times larger, “with amino acids joined to form complex primary, secondary, tertiary and quaternary structures, with post-[]translational modifications.” Chugh & Roy, *supra* note 60, at 56.

63. Chugh & Roy, *supra* note 60, at 53, 56; Price, *Regulating Secrecy*, *supra*, note 33, at 1793 (“[T]he secretive, idiosyncratic, and frequently stochastic way biologics are made hampers the development of biosimilars.”); see Blackstone & Fuhr, *supra* note 51, at 5 (discussing the complexity of manufacturing biologics and the small margin for error); see also Price, *Innovation Policy Failures*, *supra* note 8, at 345 (noting that biologicals manufacturing typically faces higher absolute costs than other drugs on both a fixed and per-unit bases).

pharmacological mechanisms.⁶⁴ The manufacturing processes of biosimilars create variability in structure and therefore cause variability in immunological responses.⁶⁵

Variability and these barriers to entry, however, are opportunities for manufacturers to reach captive markets, which is exemplified by the patent-trade secret trade-off scenario. There, the manufacturer can either withhold information as trade secrets to prevent follow-on manufacturers from reverse-engineering biologics or processes, or the manufacturer can disclose critical aspects of the process in return for patent exclusivity periods.⁶⁶ Ultimately, the manufacturer wants the patent and BLA/aBLA claims to be broad enough to protect subsequent innovation, while narrow enough to prevent subsequent biopharmaceutical manufacturers from reverse-engineering and pushing the biologic originator out of the market.⁶⁷

D. Manufacturing Innovation: The Rate-Determining Step for Biologics and Biosimilars Market Growth

Innovation requires sharing information among pioneers. In the highly regulated drug industry, manufacturers are incentivized to innovate when provided with reasonable investment-backed expectations and compensation in return for information disclosure. When biologics and biosimilars manufacturers are provided time and incentive to analyze manufacturing “drift,”⁶⁸ there will be more efficient manufacturing methods, alternative therapeutic uses, and innovative manufacturing processes, all of which will improve drug safety, efficacy, and purity.⁶⁹

64. Shein-Chung Chow et al., *Scientific Considerations for Assessing Biosimilar Products*, 32 *STAT. MED.* 370, 371–72 (2013); see also Lucio et al., *supra* note 55, at 2010; Ross & Richard, *supra* note 38, at 297.

65. Chow et al., *supra* note 64, at 375–76; Chugh & Roy, *supra* note 60, at 56 (describing how differences in manufacturing can involve structural changes in extraction, purification processes, three-dimensional environmental structure, quantity of acid-base variants, and the glycosylation profile); see also Roe, *supra* note 4, at S28 (reporting that immunogenicity and immune responses caused by these structural changes during the manufacturing process are the primary safety concerns of biosimilars prescribers).

66. See *infra* Part III.

67. Blackstone & Fuhr, *supra* note 51, at 7; see *infra* Section II.A.

68. Tkaczuk & Jacobs, *supra* note 56, at 5–6 (defining “drift” as the physiochemical variance of biologics characteristics over time).

69. McCamish & Woollett, *supra* note 4, at 407–08 (explaining that sponsors routinely change manufacturing processes when scaling, improving efficacy, or

The development and acceptance of biologics and biosimilars for cancer therapies accentuates how precision medicines depend upon a manufacturer's incentive to innovate.⁷⁰ As biologics develop, cancer treatments will be tailored to each patient and target specific characteristics of the tumor or tumor-causing agent, illustrating the accurate and precise nature of biological therapies.⁷¹

Similarly, yet not ideally, biosimilars manufacturers first determine and then compare quality target product profile (QTPP) parameters to coincide with the RPS's process.⁷² Biosimilar manufacturers possess and use process "knowledge of cell expansion, filtration, centrifugation, purification, product characterization, and . . . product stability" to meet the FDA's minimum safety and efficacy standards.⁷³ The strength of their process knowledge and reassurance of quality, safety, and efficacy is then translated to clinicians and physicians to ensure they are informed decision makers before consulting with patients.⁷⁴ Thus, the FDA can indirectly control which biopharmaceuticals—and therefore the extent of clinical trial data necessary—physicians and other health-care providers prescribe and integrate into clinical practice.⁷⁵

modernizing the process, thus providing an avenue to explore manufacturing innovation).

70. Roe, *supra* note 4, at 28–29 (“[I]ncreased use of biosimilars may be seen as a possible cost saving in the treatment of cancer, offering greater access to treatments and providing the option for treatments to be introduced earlier.”); Wehrwein, *supra* note 58 (concluding that more and more drug products overlap in indication, including biosimilars, which will offer cheaper alternatives and quality care); *see also* Lucio et al., *supra* note 55, at 2006 (describing the complexities of manufacturing processes including isolating a targeted gene, cloning and then expressing the gene). *Compare supra* Section I.C (acknowledging that incentivizing biologics variability assessments is dependent upon the target market), *with* Chugh & Roy, *supra* note 60, at 56 (“Biologics with complex production processes and the resultant heterogeneous compounds make it difficult to standardise the product, manufacture, and ensure adequate activity, integrity, and quality.”). Idealistically, biologics could become a single-treatment cure, whereby clinicians tell manufacturers the exact indication or treatment required, and the manufacturer adjusts process parameters to output the desired formulary.

71. Tkaczuk & Jacobs, *supra* note 56, at 3. For example, Trastuzumab, a biologic, is the first targeted therapy for women with HER2 overexpressed breast cancer. *Id.* at 3–4.

72. Bui et al., *supra* note 34, at 7.

73. Lucio et al., *supra* note 55, at 2006, 2009.

74. Tkaczuk & Jacobs, *supra* note 56, at 6.

75. *Id.* at 10; *see* David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 143–45 (2005)

Customers and clinicians know a biologic typically costs at least twenty times more than a small-molecule drug.⁷⁶ What they don't know is how the market will respond to biologics—i.e., whether the market will find them worth the cost—though clinical data should point consumers in the right direction.

Biosimilars require analytical comparability,⁷⁷ which must demonstrate that the biosimilar is “highly similar” without having “clinically meaningful differences . . . in terms of the safety, purity, and potency.”⁷⁸ These statutory and FDA mandates result in consumers and physicians receiving the critical data necessary for acceptance and prescription of these medicines. The FDA must therefore balance safety requirements and economic rationale for drug development⁷⁹ to ensure biosimilar manufacturers continue to explore optimal process parameter designs.⁸⁰ Enhanced safety and comparability studies allow physicians to make informed policy decisions about the administration of these new therapies;⁸¹ they also require that the manufacturing process achieve a formulation

(discussing the history of biologics and recommending a regulatory framework for the FDA to adopt regarding biologics under the Federal Food, Drug, and Cosmetic Act).

76. Ude Lu, Note, *Biologics Price Competition and Innovation Act: Striking a Delicate Balance Between Innovation and Accessibility*, 15 MINN. J.L. SCI. & TECH. 613, 633 (2014).

77. See *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25–27 (D.D.C. 1996) (upholding the FDA's authority to use the comparability process, requiring pharmacological and therapeutic equivalence).

78. 42 U.S.C. § 262(i)(2)(A)–(B) (2012); see also Chow et al., *supra* note 64, at 374.

79. Hirsch & Lyman, *supra* note 36, at 265; see also W. Nicholson Price II & I. Glenn Cohen, *Nudging the FDA*, AM. INT., Nov./Dec. 2014, at 35, 36 (highlighting the role of the FDA “in balancing the safety of drugs against their potential” treatment use).

80. These design parameters are “goalposts” that a biologicals license candidate uses to compare to the reference originator product. McCamish & Woollett, *supra* note 4, at 410. Any parameter for the biosimilar outside of the goalpost must be shown to have no clinically significant impact on the final product. *Id.*

81. Chugh & Roy, *supra* note 60, at 62 (“Evidence-based medicine and clinical experience strongly influence a physician's decision to prescribe a particular product. Physician's acceptance and subsequent prescribing of a new biosimilar product will require adequate information and evidence ensuring efficacy and patient safety.”); Lucio et al., *supra* note 55, at 2007 (noting that because bioequivalence cannot be established, health institutions and physicians will need to individually evaluate biosimilars before prescribing them); see also Tkaczuk & Jacobs, *supra* note 56, at 5 (stating that scientific societies must help evaluate biosimilar data while educating healthcare providers and providing general consensus regarding effective therapeutic uses); Roe, *supra* note 4, at 29 (maintaining that physicians act as advocates for patients and will further support biosimilars in a clinical setting once biosimilar drug mechanisms and differences in the side effect profiles are understood).

containing the least amount of other chemicals.⁸² Ultimately, a manufacturer's goals must include a more quantitative, mechanism-based understanding, and an ability to predict human health, disease, and intervention responses.⁸³

However, scientific and legal restraints force manufacturers to essentially construct manufacturing processes from scratch.⁸⁴ Accordingly, there is significant risk with uncertain and unquantifiable reward because the biosimilar manufacturing process may fail to identically replicate an originator biologic, or it may ideally produce enhanced process control and new therapeutic uses.⁸⁵ Nevertheless, rather than precise structure and physiochemical characterization, biosimilarity subsequently turns into a comparative analysis: assessing manufacturing process variability and comparing product efficacy and safety between an innovator and FOB by using QTPP parameters.⁸⁶

II. FDA EXCLUSIVITY: TAKING ADVANTAGE OF AN EXECUTIVE AGENCY'S SUPPLY OF DE FACTO MONOPOLIES

The BPCIA's dual mission of promoting innovation and accessibility of biologics creates unique opportunities for biologics manufacturers. To promote innovation, the FDA grants market and data exclusivity periods. Specifically, the twelve-year market and four-year data exclusivity periods for originator biologics prevent biosimilars or interchangeables from being approved.⁸⁷ One of the most effective opportunities innovators utilize is the FDA data exclusivity grant. While market exclusivity means "simply having no competition for a product in the marketplace," data exclusivity refers to protection of the drug and original clinical trial data, preventing manufacturers from supporting approval of their biosimilar.⁸⁸ Only a

82. Dudzinski, *supra* note 75, at 232.

83. Woodcock, *supra* note 13, at 152; *see infra* Section IV.C.2 (arguing that, because they possess first-hand process knowledge, originators are best capable of analyzing and predicting societal health improvements from current and enhanced manufacturing capabilities).

84. Price, *Innovation Policy Failures*, *supra* note 8, at 350.

85. Blackstone & Fuhr, *supra* note 51, at 5.

86. Chow et al., *supra* note 64, at 380.

87. 42 U.S.C. § 262(k)(7)(A)–(B) (2012); Lu, *supra* note 76, at 613–14.

88. Jonathan Stroud, Comment, *The Illusion of Interchangeability: The Benefits and Dangers of Guidance-Plus Rulemaking in the FDA's Biosimilar Approval Process*, 63 ADMIN. L. REV. 599, 602 nn.13–14 (2011).

biologic with a structural modification resulting in a change in safety, purity, or potency is eligible for data exclusivity.⁸⁹ But once the four-year data exclusivity grant elapses, the FDA starts accepting aBLAs.⁹⁰ These applicants piggy-back off of the approved originator's clinical trials in anticipation of the market exclusivity term expiration.⁹¹

FDA exclusivity grants provide unique and potentially stronger protection than patent exclusivity for four reasons: (1) novel biologic's composition classifications inherently cover a larger scope than a single patent; (2) currently, twelve years of exclusivity likely meets or slightly surpasses the life of the biologic's active composition patent;⁹² (3) FDA exclusivity is independent from, and in addition to, claims for patent exclusivity; and (4) FDA exclusivity inherently inhibits reverse-engineering and designing-around.⁹³ The advantages of these FDA exclusivity grants in light of their disclosure requirements are examined below with respect to originator biologics and FOB manufacturing processes.

A. *Obligations for Biological Products Market Entry*

Before a manufacturer may introduce a biological product into interstate commerce, it must receive a biologics license authorized under the Public Health Service Act ("PHSA").⁹⁴ Before 2010, the FDA granted biologics licenses only under section 351(a) of the PHSA for pioneers (i.e. innovators) and for select products and hormones under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA).⁹⁵

In 2010, the BPCIA implemented a balance between societal health implications and incentivizing market growth through both increased

89. 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc) (2012).

90. U.S. DEP'T OF HEALTH & HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY: REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION 351(A) OF THE PHS ACT 1 (Aug. 2014), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>.

91. *Id.* at 2–3.

92. As prior art and manufacturing methodology improves, process innovations are likely to require less testing and validation; thus, patents can be applied for earlier in the biologics development life-cycle, and exclusivities are thereby likely to extend past patent protection.

93. Lu, *supra* note 76, at 623–24.

94. Public Health Service Act, 42 U.S.C. §§ 201–300; 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, 285 (2011).

95. Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–99; Epstein, *supra* note 94, at 285, 294; *see supra* note 39.

consumer access and incentivized innovation. The BPCIA revised section 351(a) to create a stand-alone pathway for abbreviated applications under section 351(k) of the PHSA.⁹⁶ With the change, the FOB applicant must show that “the biological product . . . is safe, pure, and potent.”⁹⁷ However, the safety, purity, and potency is controlled directly by the biological product’s manufacturing process. Thus, “the facility in which the biological product is manufactured, processed, packed, or held [must meet] standards designed to assure that the biological product continues to be safe, pure, and potent.”⁹⁸

The BPCIA (1) established standards for application and approval,⁹⁹ (2) provided a term of data exclusivity,¹⁰⁰ and (3) established a scheme for handling patent disputes.¹⁰¹ However, the BPCIA imposes a new disclosure requirement for license holders and imposes requirements on both pioneer biologic and biosimilar manufacturers:¹⁰² for instance, it requires pioneer biologic manufacturers to provide applicants with a list of patents it believes “could reasonably be asserted” as infringed with respect to the pioneer product.¹⁰³ The BPCIA requires this exchange to be in good

96. 42 U.S.C. § 262(k); Epstein, *supra* note 94, at 286. The BPCIA stipulates that a manufacture may not apply for a biosimilars license until four years after—and the biosimilar cannot be approved until twelve years after—the reference biologic is approved. Strand & Cronstein, *supra* note 36, at 220.

97. 42 U.S.C. § 262(a)(2)(C)(i)(I).

98. § 262(a)(2)(C)(i)(II).

99. Tkaczuk & Jacobs, *supra* note 56, at 5 (arguing that the goal of biosimilar development should be to show sufficient similarity in composition, biological activity, and pharmacokinetics to allow existing efficacy and safety data to be used, thus resulting in a more efficient development and approval process).

100. McCamish & Woollett, *supra* note 4, at 408 (highlighting the twelve year period of exclusivity for innovator biologics provided by the BPCIA).

101. § 262(l)(1)(F).

102. Chugh & Roy, *supra* note 60, at 60–61 (noting that the aBLA for highly similar biological products requires a demonstration of the same “mechanism of action, route of administration, dosage form, and potency” compared to the innovator product); Tucker & Wells, *supra* note 39, at 101 (listing the steps at which a pioneer must share information with a follow-on manufacturer, including: follow-on application disclosure, first pioneer response, follow-on response, second pioneer response, negotiations and initial litigations, and notice of commercial marketing).

103. § 262(l)(3)(A)(i) (requiring the RPS, no later than sixty days after receiving applicants information, to provide “a list of patents for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted by the reference product sponsor”); *see also* § 262(l)(3)(B) (providing that the applicant may proactively provide the RPS with “a list of patents to which the subsection (k) applicant believes a claim of patent infringement could reasonably be asserted” but

faith so that the applicant and RPS agree on which patents will be the subject of any infringement action.¹⁰⁴ This is a critical step in process protection for the manufacturer: it must decide whether trade secrecy or patentability provides the best value for protection.¹⁰⁵ Because confidential manufacturing information would be provided by the applicant to the RPS,¹⁰⁶ both the RPS and the FOB applicant must determine the value of their manufacturing processes (and clinical trials) prior to any exclusivity grant expiration. Additional considerations relevant to the approval process for biologics and FOB include “the timing of application submission and the duration of market exclusivity for originator reference products”;¹⁰⁷ furthermore, the BPCIA does not operate retroactively with respect to any data submitted prior to its enactment.¹⁰⁸

must provide a statement regarding why the applicant believes the patent is invalid, unenforceable, or will not be infringed by the biological).

Patents provide a piece-meal description, like pieces of a puzzle, toward a determination of infringement. Only the potential infringer knows what the whole puzzle looks like, and the challenging party must analyze each piece to determine whether it fits within this puzzle or whether it is part of a puzzle of its own. Essentially, real-time analysis of the process is required for this determination, exemplified by the fact that science currently cannot classify, with sufficient particularity, all attributes and structures of a biologic. See Robin Feldman & W. Nicholson Price II, *Patent Trolling: Why Bio and Pharmaceuticals Are at Risk*, 17 STAN. TECH. L. REV. 773, 803 (2014) (discussing the difficulty in assessing patent infringement because of the propensity for trade secrecy). But see W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 526–27, 555 (2014) [hereinafter Price, *Making Do in Making Drugs*] (describing the statutory rebuttable presumption of infringement in favor of the patent holder, if the plaintiff shows “(1) that a substantial likelihood exists that the product was made by the patented process, and (2) that the plaintiff made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine” (quoting 35 U.S.C. § 295)). Furthermore, 35 U.S.C. § 271 provides a safe harbor of sorts, stating indirectly that there is no patent infringement for using a product from a patented manufacturing process for the development of a related biologic, which enables the generic to be placed on the market as soon as the patent expires. 35 U.S.C. § 271(e)(1).

104. Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, § 7002(a)(2), 124 Stat. 119, 804–21 (2010). However, if there is no agreement between parties as to which patents shall be the subject of an infringement action, the RPS may not exceed the number of patents listed by the applicant. 42 U.S.C. § 262(l)(5).

105. See *infra* Section III.B.

106. 42 U.S.C. § 262(k)(1)–(2); see *infra* text accompanying note 122.

107. Lucio et al., *supra* note 55, at 2008.

108. Epstein, *supra* note 94, at 304.

Exclusivity periods balance the interests of the patent holder with societal access and health implications. They provide valuable time for the patent holder to assess a biopharmaceutical's price necessary for recovering its initial investment.¹⁰⁹ Indirectly, they accelerate the competition's entry into the biological market¹¹⁰—with procedures by which manufacturers can formally resolve patent negotiations¹¹¹—and provide time for the RPS to identify areas of improvement for potential patent extensions.¹¹² During the data exclusivity period, the FDA cannot approve a similar or identical drug formulation that relies on the RPS's data.¹¹³ However, the data exclusivity period does not preclude FOB sponsors from conducting independent research and clinical trials. Effectively similar to the exclusionary right in patent law, data exclusivity blocks competition and creates artificial scarcity.¹¹⁴

Lastly, the RPS may be eligible for an additional subsequent data exclusivity period if an existing product is altered such that it becomes “new” and has the ability to improve disease treatment.¹¹⁵ Three primary authors of the BPCIA encouraged a liberal stance regarding what constitutes a “new” product, and if that position is adopted, structural changes would be considered “new” and therefore rewarded exclusivity periods in the future.¹¹⁶

B. Regulatory Threshold Standards for Approval of a Follow-on Biologics

Generic products, and specifically biosimilars, can substantially reduce the costs for patients and taxpayers.¹¹⁷ These cost reductions primarily stem from piggy-backing upon RPS's clinical trials and data. Using current analytical techniques, biosimilar manufacturers must compare the safety and efficacy impact of the innovator product to the reference biological product, instead of assessing how process

109. *Id.* at 286; *see also* Price & Cohen, *supra*, note 79, at 35 (“[The FDA] also controls the accelerator and brake pedals on drug development and innovation through its control of market exclusivity for approved new drugs.”).

110. Epstein, *supra* note 94, at 286.

111. Lucio et al., *supra* note 55, at 2008.

112. *See* Blackstone & Fuhr, *supra* note 51, at 6; Bui et al., *supra* note 34, at 8–9.

113. 42 U.S.C. § 262(k)(7)(A); *see* Gaudry, *supra* note 22, at 592.

114. Sorscher, *supra* note 17, at 294.

115. Gaudry, *supra* note 22, at 594.

116. Letter from Rep. Anna G. Eshoo, Rep. Jay Inslee, and Rep. Joe Barton to Food and Drug Administration (Dec. 21, 2010), <http://www.hpm.com/pdf/EIB%20Ltr%20FDA%20DEC%202010.pdf>.

117. *See* Stroud, *supra* note 88, at 605.

changes correlate to the final product.¹¹⁸ FOB applicants must demonstrate four criteria: (1) FOB and reference biologic product are biosimilar; (2) FOB and reference biologic product employ the same mechanism of action for the applicable condition; (3) FOB and reference biologic product share the same conditions of use, route of administration, dosage form, and strength; and (4) the facility in which the FOB is manufactured, processed, packed, or held meets safety, purity, and potency standards.¹¹⁹ If sameness is proven, additional clinical trials for safety would not be needed; additionally, historical human use provides evidence of safety.¹²⁰

Follow-on biologics capitalize on the abbreviated approval pathway for both biosimilars and interchangeable biological products.¹²¹ Originator biological product applicants must show “the FDA that its process reliably produces a pure and therapeutically effective biologic; to the extent that the process defines the product, [it] must fully lay out its process to assist the FDA to understand the product seeking approval.”¹²² Biosimilars require a demonstration of comparability while small-molecule generics require a demonstration of bioequivalence.¹²³ Biocomparability or biosimilarity is derived

118. Price, *Regulating Secrecy*, *supra* note 33, at 1796. Comparative analytical characterization may lead to one of four assessments within the development-phase continuum: (1) not similar, illustrating differences in results of analytical characterization leading to further development through 351(k) not being recommended; (2) similar, illustrating further information needed to determine whether differences are within acceptable range to consider proposed biosimilar product to be highly similar; (3) highly similar, illustrating proposed biosimilar meets the statutory standard for analytical similarity, with residual uncertainty capable of being resolved with targeted and selective animal and/or clinical studies; and (4) highly similar with fingerprint-like similarity, illustrating the proposed biosimilar meets statutory standards for analytical similarity based on a high level of confidence and analytical similarity, with residual uncertainty capable of being resolved with targeted and selective animal and/or clinical studies. U.S. DEP’T OF HEALTH & HUMAN SERVS., CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT 5–6 (Dec. 2016), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf>.

119. 42 U.S.C. § 262(k)(2)(A)(i) (2012); *see also* Gaudry, *supra* note 22, at 596 (describing the requirements for FOB applications).

120. § 262(k)(4).

121. § 262(i)(2)(B), (k)(2).

122. Price, *Regulating Secrecy*, *supra* note 33, at 1803.

123. Li et al., *supra* note 57, at 3; *see* McCamish & Woollett, *supra* note 4, at 409 (correlating attributes of the product to safety, purity, and potency for the United States, and quality, safety, and efficacy for Europe). Thus, the development of

from analytical studies (establishing similarity), as well as animal studies (assessing toxicity) and clinical studies (assessing immunogenicity and pharmacokinetics or pharmacodynamics) to determine if a biologic is safe and effective.¹²⁴

Interchangeable biologics on the other hand, require more extensive showings but provide additional incentives. Interchangeable biologics (1) must meet the standards for biosimilarity, (2) should “produce the same clinical result as the reference product in any given patient,” and (3) can be switched between the FOB and originator without presenting any ancillary safety or efficacy risks.¹²⁵ If the FOB is deemed interchangeable with the reference product, a pharmacist may automatically substitute or propose substitution without intervention from the prescribing health-care provider.¹²⁶ Important to prescribing physicians and pharmacists is that there are no additional safety or efficacy risks when switching between the original and interchangeable biological product; however, these risk examinations require additional studies—with, at best, potential exclusivity advantages.¹²⁷ Due to the current scientific state of biologics design and manufacturing,¹²⁸ the FDA has not approved any interchangeable biologics product, and applicants are more likely to seek biosimilar approval prior to seeking

biosimilars requires iterative manufacturing process developments using elements of quality by design to produce the QTPP of the reference biologic. Bui et al., *supra* note 34, at 9.

124. Gaudry, *supra* note 22, at 598.

125. 42 U.S.C. § 262(k)(4)(A)(ii); *see also* § 262(i)(2)(B), (i)(3); Ross & Richard, *supra* note 38, at 296; Tucker & Wells, *supra* note 39, at 100. “Interchangeability is important because it provides for a period of market exclusivity as well as for automatic substitution of the interchangeable for the approved biologic without intervention from the prescribing physician.” Patricia Fitzpatrick Dimond, *FDA Releases Biosimilars Guidelines to Little Fanfare*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Mar. 15, 2102), <http://www.genengnews.com/gen-articles/fda-releases-biosimilars-guidelines-to-little-fanfare/4035>. However, the FDA has acknowledged that it is scientifically difficult to currently meet interchangeable data requirements. *Id.*

126. 42 U.S.C. § 262(i)(3).

127. The standards for interchangeability are higher than biosimilarity because an interchangeable biologic can be substituted with the reference product without acknowledgement by a healthcare provider. Tkaczuk & Jacobs, *supra* note 56, at 7; Reinke, *supra* note 61.

128. Price & Rai, *supra* note 42, at 188 (“[F]undamental knowledge has not advanced to the point where product characteristics can fully be identified and characterized through analysis of the final product.”).

approval for an interchangeable biological product.¹²⁹ The Federal Trade Commission estimates that development of an FOB would take between eight and ten years and cost \$100 to \$200 million; and, because these FOBs will primarily be biosimilars, sponsors will miss out on first interchangeable FOB exclusivity periods.¹³⁰

With the enactment of the BPCIA, originator and innovator biologics manufacturers are incentivized to invest in long-term biological manufacturing process improvements.¹³¹ “[B]iosimilars . . . can make the same headroom that generics made in the past”¹³² without the patent cliff fear that plagued the generics market, providing an additional incentive to enter the biosimilars market. The FOB applicant can submit its aBLA four years after the reference

129. McCamish & Woollett, *supra* note 4, at 411 (“Although an initial application in the United States for a biosimilar can be for an interchangeable product, it is expected that most sponsors will seek to establish biosimilarity first and then supplement their dossier with additional data to support interchangeability.”); Tkaczuk & Jacobs, *supra* note 56, at 8 (“Interchangeability therefore requires an expectation that the safety and efficacy risk is not greater than the reference product not only in the population but at the individual patient level, and this is, necessarily, a very high standard that may be difficult to establish on a scientific basis.”); *see also* Stroud, *supra* note 88, at 626 (noting that higher interchangeability standards may mean the costs do not outweigh the benefits of generic status).

130. FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION iii, 10 (2009), <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf>; *see also* 42 U.S.C. § 262. Currently, investments pursuing interchangeability are not fiscally justified due to the scientific state of biologics comparability, and the uncertainty of physician—as well as consumer—acceptance of biologics.

131. *See* U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 7 (Apr. 2015) [hereinafter HHS, SCIENTIFIC CONSIDERATIONS], <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf> (encouraging biosimilar sponsors to use a “stepwise approach” in developing and testing a biosimilar); U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY OF A THERAPEUTIC PROTEIN PRODUCT TO A REFERENCE PRODUCT 10–16 (Apr. 2015) [hereinafter HHS, QUALITY CONSIDERATIONS], <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf> (discussing factors sponsors should consider during the development and testing of a biosimilar); Chugh & Roy, *supra* note 60, at 62 (concluding that biologics’ complexity requires “ongoing risk-benefit assessment and effective post-marketing pharmacovigilance to ensure product safety and efficacy”); Huzair & Kale, *supra* note 38, at 251.

132. Wehrwein, *supra* note 58. The biosimilar class is a much more attractive investment, so headroom must be made in the form of long-term value as opposed to short-term price differential. *See Biobetters Versus Biosimilars*, *supra* note 4 (comparing the twenty-five percent to the seventy-to-ninety percent price erosion of biosimilars versus small molecule generics).

biological product is licensed.¹³³ Thus, the FOB has ample time—eight years after the expiration of the four-year data exclusivity period—to obtain product approval prior to the expiration of the RPS’s market exclusivity period.

FOB applicants have been hesitant to use the biosimilars application process, as they continue to encounter significant risks and barriers to entry. The aBLA for “highly similar” biological products follows the pathway outlined by section 351(k) of PHSA.¹³⁴ Examiners use a “totality-of-the-evidence” approach to evaluate the biologics application.¹³⁵ However, these requirements do not sufficiently assist physician decision-making processes, prompting applicants to push-back.¹³⁶ Notably, the first aBLA was not approved until 2015.¹³⁷

The design of the clinical trial is the most important aspect for approval of the aBLA¹³⁸ and uses a step-wise approach¹³⁹ for assessing trial progress.¹⁴⁰ Conducting clinical trials amount to about half of drug approval costs.¹⁴¹ The step-wise approach also allows investors to make critical investment decisions along the way to assess and add value to the biosimilarity determination.¹⁴² However, a sentiment

133. 42 U.S.C. § 262(k)(7)(B).

134. See 42 U.S.C. § 262(k); HHS, QUALITY CONSIDERATIONS, *supra* note 131, at 1; HHS, SCIENTIFIC CONSIDERATIONS, *supra* note 131, at 9.

135. Chow et al., *supra* note 64, at 362; Lucio et al., *supra* note 55, at 2009.

136. For examples of the lack of confidence in gaining product approval and in the requirements for approval, see Anna Rose Welch, *Are Emerging U.S. Biosimilar Policies at Risk of Alienating Physicians?*, BIOSIMILAR DEV. (Apr. 5, 2016), <http://www.biosimilardevelopment.com/doc/are-emerging-u-s-biosimilar-policies-at-risk-of-alienating-physicians-0001>; Anna Rose Welch, *How to Approach U.S. Physicians About Biosimilars*, BIOSIMILAR DEV. (Nov. 21, 2016), <http://www.biosimilardevelopment.com/doc/how-to-approach-u-s-physicians-about-biosimilars-0001>.

137. Janet Woodcock, *Biosimilar Implementation: A Progress Report from FDA*, FOOD & DRUG ADMIN. (Sept. 17, 2015), <http://www.fda.gov/NewsEvents/Testimony/ucm463036.htm>.

138. McCamish & Woollett, *supra* note 4, at 412 (discussing that the sponsor of a biosimilar must have a thorough understanding of how to characterize the originator product so suitable tests are used and the clinical trials are designed effectively).

139. Li et al., *supra* note 57, at 3 (intending biosimilarity analysis to be product-specific, “with each step serving to resolve as much remaining uncertainty as possible”).

140. “Randomized controlled trials (RCTs) remain the gold standard for assessing the efficacy and safety of new drugs.” Dranitsaris et al., *supra* note 49, at 481; see also Strand & Cronstein, *supra* note 36, at 220 (indicating that the FDA uses a stepwise, risk-based approach to determine the extent of residual uncertainty that should be addressed by more animal and clinical studies).

141. Sorscher, *supra* note 17, at 293–94.

142. Li et al., *supra* note 57, at 7.

many applicants likely agree with, is that the FDA must expand the role of clinical pharmacology studies.¹⁴³ In other words, the burden on the FOB applicant remains too high, and the FDA should consider data directly impacting patients as opposed to theoretical pharmacokinetics and pharmacodynamics studies.¹⁴⁴

After a “patent dance,”¹⁴⁵ the approval process concludes with the originator’s reference biological product scope and the innovator’s FOB application.¹⁴⁶ During the dance, the applicant clearly has the higher degree of risk: the data exclusivity period has elapsed and the market exclusivity period of the RPS has already been granted. *Pfizer Inc. v. Dr. Reddy’s Laboratories, Ltd.*¹⁴⁷ illustrates that the generic drug manufacturer “must walk a fine line” by achieving similarity but avoiding patent infringement.¹⁴⁸ Thus, the applicant must make a risky

143. The FDA has broad discretion inherently built into a “highly similar” determination that could allow it to give more weight to these studies. See Stroud, *supra* note 88, at 625 (providing an example of how permissive the FDA may be: “[t]he FDA can waive toxicity or certain Phase II and Phase III trials upon a ‘good enough’ showing of chemical similarity”).

144. Reinke, *supra* note 61.

145. The patent dance is a procedure, after the biosimilar application has been submitted to the FDA, where the applicant and RPS resolve patent disputes. Louis E. Fogel & Peter H. Hanna, *The Biosimilar Regulatory Pathway and the Patent Dance*, JENNER & BLOCK (Dec. 2014) https://jenner.com/system/assets/publications/13837/original/The_Biosimilar_Regulatory_Pathway_and_the_Patent_Dance.pdf (noting that the patent dance involves strictly timed and sequential rounds of exchanging information); see also Jeff Overley, *Biosimilar Notice Always Mandatory*, *Fed. Circ. Rules*, LAW360 (July 5, 2016, 1:05 PM), <http://www.law360.com/articles/792580/biosimilar-notice-always-mandatory-fed-circ-rules> (explaining that the exchanging of intellectual property information is meant to streamline patent litigation). The Federal Circuit ruled that a 180-day notice provision in the BPCIA is required even if the biosimilar makers participate in the patent dance. *Id.* Because the 180 days’ notice is required following FDA approval, reference product sponsors are provided time to prepare a motion for preliminary injunction and have it decided prior to the biosimilar’s product launch. *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1066 (Fed. Cir. 2016), *cert. denied*, No. 16-332, 2016 WL 4944497 (U.S. Dec. 12, 2016); Robert E. Colletti & Daniel G. Worley, *Sandoz Requests U.S. Supreme Court Interpretation of the Biologics Price Competition and Innovation Act in Amgen Inc. v. Sandoz Inc.*, FROMMER LAWRENCE & HAUG LLP (Feb. 18, 2016), <http://www.flhlaw.com/insights/Detail.aspx?news=31436f18-c433-4829-abee-cbc28b937129&>.

146. In *Sandoz v. Amgen*, a biosimilar maker could not file a patent suit unless and until the parties had danced the Patent Dance (a strict jurisdictional bar). 773 F.3d 1274, 1278 (Fed. Cir. 2014).

147. 359 F.3d 1361 (Fed. Cir. 2004).

148. Dudzinski, *supra* note 75, at 210. Norvasc attempted to rely on Pfizer’s data to support FDA approval of its aNDA by arguing that an intermediate ingredient

decision by determining what manufacturing process information to patent and disclose and what information to conceal as a trade secret.¹⁴⁹ This determination must be made on a case-by-case basis when analyzing exactly what the RPS has claimed and how the innovator can subsequently penetrate the biopharmaceutical market.

III. PATENT EXCLUSIVITY: BIOLOGICAL PRODUCTS AND THE RIGHT TO EXCLUDE

Patent breadth and licensing opportunities help applicants navigate the patent-trade secret scenario. If a patent is too broad, it may accidentally or strategically cover claims an originator may not have developed but were ripe for licensing.¹⁵⁰ The interplay between granted patents and applicant claims is exemplified in the blocking patent scenario: two patents block each other when one patentee has a broad patent on an invention and another has a narrower patent on some improved feature of that invention. The broad patent dominates the narrower one. In such a situation, the holder of the narrower patent needs a license from the dominant patent holder to practice the improved invention.¹⁵¹ The particular improved feature claimed in the narrower patent, however, cannot be practiced by the dominant patent holder without a license from the narrower patent holder.¹⁵²

An invention or innovation is eligible for patenting after the inventor produces a description that enables one skilled in the art to practice the invention.¹⁵³ Patents provide their own twenty-year exclusivity periods.¹⁵⁴ But, with respect to biologics manufacturing

(amlodipine maleate) fell outside the scope of Pfizer's patent. *Pfizer*, 359 F.3d at 1365, 1367 (holding that the extended period of a patent covers not only the active ingredient in an approved drug but also intermediary ingredients that are critical to the process).

149. See *infra* Part IV.

150. However, this may raise enablement issues. See 35 U.S.C. § 112(a) (2012) ("The specification shall contain a written description . . . in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use . . . the invention.").

151. *Merges & Nelson*, *supra* note 7, at 860–61.

152. *Id.* An owner of a patent with composition claims can assert the patent against an inventor who makes the molecule by another process, even if the follow-on process is much more efficient. *Feldman & Price*, *supra* note 103, at 791–92 (explaining that inventing around a blocked technology in the biopharma industry requires high costs due to the strength of the patents established by FDA's regulatory apparatus).

153. 35 U.S.C. § 112.

154. § 154(a)(2). The twenty-year patent term begins when the patent application is filed. *Id.* The average length of time required post-patent and pre-aBLA is typically seven-and-a-half to eight years. *Sorscher*, *supra* note 17, at 295. As science

processes, strong patent protection is not always available. Therefore, the exclusivity period must provide the manufacturer with sufficient incentive to disclose valuable biologics process information. Because one patent can produce upwards of ninety percent of a manufacturer's revenue, manufacturers must decide exactly what information to disclose and how to claim their process while ensuring they reap all benefits from a robust patent and subsequent monopoly.

A patent prevents others from making, using, offering to sell, or selling the patented invention.¹⁵⁵ Patent applications have specific disclosure requirements, embodied in 35 U.S.C. § 112, which include: describing the claimed invention in sufficient detail such that (1) "one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention" and (2) one skilled in the art can make and use the application's defined claims.¹⁵⁶ In other words, a patent must "particularly point[] out and distinctly claim[]" the invention.¹⁵⁷ A patent's term may extend beyond any FDA exclusivity period; because additional clinical trials are incentivized with FDA approval extensions, biologics manufacturers can test new methods and tools of manufacture within the scope and duration of previously patented claims.¹⁵⁸ Furthermore, patents offer protection capabilities not available under the BPCIA, especially with respect to manufacturing process alterations and potential new therapeutic uses stemming from process changes.

Biologic drugs having larger, more complex structures than small-molecule drugs illustrates the additional difficulties within patent protection of biological products. There is more potential for design-arounds: an RPS cannot broaden its patent to incorporate minor design-arounds or encompass claims not originally enabled by the

develops, this duration will likely shorten and the manufacturer will need more incentive to pursue aBLA exclusivity grants.

155. § 271(a).

156. U.S. PAT. & TRADEMARK OFF., MPEP §§ 2163, 2164 (9th ed. Rev. 7, Nov. 2015) [hereinafter MPEP].

157. 35 U.S.C. § 112(b). Acting as a lever to spur scientific advancement, the degree of distinctly claiming an invention inherently changes as scientific achievements enable manufacturers to piece together how process parameters correlate with final product attributes.

158. If the operational regulatory philosophy is to provide society with a greater guarantee of safety, the FDA would necessitate clinical trials. Dudzinski, *supra* note 75, at 232. Because clinical trials are necessary for any change in safety, efficacy, or purity, this provides manufacturers with an opportunity to show manufacturability and thus patentability.

patent's specification.¹⁵⁹ Nevertheless, the cost of designing the manufacturing process, instituting clinical trials, and obtaining FOB product approval acts as a barrier in itself—fewer parties will challenge the validity of its patents (compared to small-molecule RPSs) and fewer instances of prior art establishing anticipation or obviousness, ensuring more patents remain valid.¹⁶⁰ Due to these inherent barriers and the ability to threaten enforcement of patents covering biologics after the twelve-year exclusivity period, patents will continue to play a governing role in protection, disclosure, and innovation for biologics manufacturers.

A. *Claiming User Rights for Biologics and Biosimilar Manufacturers*

Pioneer biologics and FOB sponsors have similar disclosure concerns for patentable subject matter and subsequent claim scope requirements. A Biologic's patent application claims typically fall in one of three categories: (1) composition claims,¹⁶¹ (2) method/process claims,¹⁶² and (3) source claims.¹⁶³ Because biologic products are closely correlated to their manufacturing method/process, composition claims and method/process claims are intertwined.¹⁶⁴ Therefore, when an applicant is deciding whether to

159. See 35 U.S.C. § 132(a); MPEP § 2163.06.

160. Gaudry, *supra* note 22, at 617.

161. Price, *Making Do in Making Drugs*, *supra* note 103, at 525 (“[A] patent on the drug's active ingredient allows the patentee to exclude others from making, selling, or using the drug for any use, even those uses not specifically envisioned by the patentee.”).

162. Price, *Regulating Secrecy*, *supra* note 33, at 1807 (“[M]ethod patents are particularly hard to enforce in part because methods are kept secret, so infringement frequently goes unobserved.”). *But see id.* (“If firms effectively disclose their methods, observing patent infringement becomes easier, which increases incentives to pursue patents in the first place.”). “[P]rocess elements should not limit the scope of a claim to a novel product . . . because process elements cannot impart novelty to a composition claim directed to a known product” Dmitry Karshedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109, 121–22 (2010) (citing *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1583 (Fed. Cir. 1991)).

163. See generally Price, *Regulating Secrecy*, *supra* note 33.

164. Composition claims, however, have traditionally been considered much more powerful than process claims. These types of claims may prove to provide broad patent protection as well as information sharing and ultimately can aid innovation in the field. Feldman & Price, *supra* note 103, at 792. Composition claims are uniquely appropriate for claiming certain products of biotechnology “when the product is new and unobvious, but has a process-based limitation.” *Atl. Thermoplastics Co. v. Faytex Corp.*, 974 F.2d 1279, 1284 (Fed. Cir. 1992) (Newman, J., dissenting) (citing *E.P.*

protect a novel and nonobvious claim, biologics and biosimilars manufacturers have a significant incentive to determine realistic ROI by analyzing patent and trade secrecy protection enforcement capabilities.¹⁶⁵ Furthermore, when a successful drug sponsor is awarded a guaranteed limited market monopoly, the company will more easily justify the expense and risk of R&D.¹⁶⁶

B. *Obtaining the Right to Exclude*

Biologics manufacturers constantly evaluate the value of their manufacturing processes. Manufacturing drift is an opportunity for biologics manufacturers to reassess their manufacturing processes. These necessary reassessments during exclusivity periods provide opportunities for manufacturers to determine how to improve their process. Therefore, an assessment of patentable subject matter and trade secret protection guide each applicants' level of disclosure; because patent law prevents inventors from receiving both patent and trade secret protection, a biologics manufacturer must also evaluate which mode of protection best suits its innovation and corporate-market goals.¹⁶⁷

1. *Patentability hurdles for biologics and biosimilars*

Patentable subject matter is a baseline criterion that each manufacturer must assess prior to pursuing protection and/or exclusivity grants. Patentable subject matter is "any new and useful process, machine, manufacture, or composition of matter, or any new

Mirabel, *Product-by-Process Claims: A Practical Perspective*, 68 J. PAT. & TRADEMARK OFF. SOC'Y 3 (1986)).

165. See 35 U.S.C. § 102 (2012) (setting out the conditions for patentability based on novelty); § 103 (setting out the conditions for patentability based on non-obvious subject matter). Patent law encourages disclosure of new discoveries in return for limited grants of exclusivity, while trade secret laws appear to encourage concealment of new discoveries, allowing concealed knowledge to be exploited for an indefinite period of time; see also *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480–81 (1973). For products whose structure cannot be determined precisely, process limitations may be the only choice for ensuring the claim meets the enablement requirement.

166. Gaudry, *supra* note 22, at 590. The incentive to innovate (or incentive to commercialize), which includes the entire process of research, development, and turning an idea into an economically viable finished product, is commonly recognized as one of three patent/economic theories. CRAIG ALLEN NARD, *THE LAW OF PATENTS* 34–36 (4th ed. 2016). The other two theories are the incentive to invent and the incentive to disclose. *Id.*

167. J. Jonas Anderson, *Secret Inventions*, 26 BERKELEY TECH. L.J. 917, 923 (2011).

and useful improvement.”¹⁶⁸ Patents grant their holder exclusive rights for a fixed period.¹⁶⁹ Seemingly anticompetitive, patents represent a legal “right to exclude,” producing a limited monopoly.¹⁷⁰

The patent application is first received by the USPTO, where a *prima facie* determination is made as to the sufficiency of the application’s completion.¹⁷¹ Thus, the USPTO determines the scope of a patent, which influences the development of technology—both regarding standards of current applicant material and future development upon disclosed information.¹⁷²

There are essentially four requirements or hurdles for patentability and approval of the patent application: (1) statutory subject matter,¹⁷³ (2) non-obviousness,¹⁷⁴ (3) novelty,¹⁷⁵ and (4) descriptive

168. 35 U.S.C. § 101. Inventors cannot patent laws of nature, natural phenomena, or abstract ideas; however, courts have struggled with what constitutes an abstract idea and what constitutes an inventive concept because “any claim, described at a certain level of generality, can be challenged as directed to an abstract idea.” *Fairfield Indus. v. Wireless Seismic, Inc.*, No. 4:1-CV-2972, 2014 WL 7342525, at *4 (S.D. Tex. Dec. 23, 2014); Steven M. Amundson, *The Supreme Court’s Decision in Alice Corp. v. CLS Bank Has Taken a Heavy Toll on Patents for Computer Related Inventions*, FROMMER LAWRENCE & HAUG LLP (Feb. 16, 2016), <http://www.flhlaw.com/insights/Detail.aspx?news=2854e313-72d2-4a5c-a27a-4a9a10ff34e5&>. After the 2014 decision in *Alice Corp. v. CLS Bank*, 134 S. Ct. 2347 (2014) (holding that an abstract idea is not patentable), about seventy percent of challenges for failure to claim patent-eligible subject matter have succeeded. Amundson, *supra*.

169. Epstein, *supra* note 94, at 288.

170. *Id.* at 315; Brian J. Love & Christopher B. Seaman, *Best Mode Trade Secrets*, 15 YALE J.L. & TECH. 1, 5 (2012).

171. *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997) (holding that “the language of the claim frames and ultimately resolves all issues of claim interpretation”), *amended by* 131 F.3d 1009 (Fed. Cir. 1997).

172. *See Merges & Nelson, supra* note 7, at 840, 842; *supra* notes 156–57 and accompanying text.

173. 35 U.S.C. § 101. Statutory subject matter determines what can and cannot be patented, with a societal benefit or usefulness nexus.

174. § 103. “‘Section 101 is not so narrow’ as to prevent the patenting of any innovative method that acts on something naturally occurring.” David A. Zwally, *The Federal Circuit Clarifies the Scope of § 101 in Pharmaceutical Related Patents*, FROMMER LAWRENCE & HAUG LLP (July 5, 2016), <http://www.flhlaw.com/The-Federal-Circuit-Clarifies-the-Scope-of-101-in-Pharmaceutical-Related-Patents-07-11-20161>. Thus, even if you are the first inventor to conceptualize and reduce to practice, the invention must be a large enough leap or difference from what came before that patenting is warranted and deserved.

175. § 102. Novelty is an assessment of whether an invention has been done before. There are inherent statutory and priority bars encompassed in the novelty provision: even if you invent something new, there may be something an applicant has done, such as public disclosure of the invention’s particulars before securing the

requirements.¹⁷⁶ The descriptive requirement¹⁷⁷ is most important for biological sponsors and innovators because it mandates public disclosure of the best mode¹⁷⁸ contemplated at the time of application.¹⁷⁹ Courts tend not to treat patents that merely improve prior art as equivalents.¹⁸⁰ However, when a patent represents a pioneer, novel invention with societal value and impact, courts tend

patent, to preclude its ability to patent; and when two patents cover the same claims, only one can be said to have priority over the other.

176. § 112. Descriptiveness requires adequate disclosure and claiming, embodied by three requirements: enablement, written description, and definiteness. In other words, an applicant must describe the invention with enough definiteness so “as to enable any person skilled in the art to which it pertains . . . to make and use” the invention. *Id.*

177. Love & Seaman, *supra* note 170, at 5 (stating that enablement “requires a patentee to provide enough information ‘for a person skilled in the art to make and use the invention without undue experimentation’” (quoting *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988)). Reproducibility and operability of the process play a critical role in determining whether the manufacturer will disclose enough information for enablement, yet withhold critical process parameters from being analyzed and used by another manufacturer/reverse-engineer.

178. *See id.* (explaining that best mode is “the best mode contemplated by him, as of the time he executes the application, of carrying out the invention” and “helps fill the gap between enablement’s minimum disclosure and the inventor’s own knowledge about her preferred implementation of the invention. [The] purpose ‘is to restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of the inventions they have in fact conceived’” (quoting *Teleflex, Inc. v. Ficoso N. Am. Corp.*, 299 F.3d 1313, 1330 (Fed. Cir. 2002)). *But see* S. 515 111th Cong. § 14 (2009) (providing that a “failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable”). Even though the bill died, both chambers passed bills in 2011 that were substantively identical to the 2009 Senate bill regarding best mode. H.R. 1249, 112th Cong. § 15 (2011) (as passed by House, June 23, 2011); S. 23, 112th Cong. § 15 (2011) (as passed by Senate, Mar. 8, 2011). The Senate ultimately approved the House’s version of patent reform without amendment on Sept. 8, 2011. 157 Cong. Rec. S5442 (daily ed. Sept. 8, 2011) (approved 89–9).

179. 35 U.S.C. § 112; *see also* Love & Seaman, *supra* note 170, at 5 (detailing that enablement has both subjective and objective components: the subjective component asks “whether the inventor considered a particular mode of practicing the invention to be superior to all other modes at the time of filing’ the application,” and then, if so, the objective question becomes whether the applicant “adequately disclose[d] the mode . . . considered to be superior” (quoting *Teleflex*, 299 F.3d at 1330)).

180. *Merges & Nelson*, *supra* note 7, at 860. However, “short of uncovering a smoking gun in discovery, an accused infringer often cannot tell ex post that a trade secret asserted today was the patentee’s best mode years prior.” Love & Seaman, *supra* note 170, at 13.

to provide broader ranges of entitlement.¹⁸¹ When an innovation represents a wholly novel formulation, clearly progressing the art of science, it will receive a larger scope of patent protection.¹⁸²

2. *Premise of trade secrecy while adjusting to the AIA*

Biologics manufacturing processes are large and complex systems where small changes may eliminate effectiveness or raise safety concerns. Similarly, claimed or patented biologics manufacturing processes restrict protection of manufacturing to precisely the claimed process, making reverse-engineering or design-around claims easy to discover. Trade secrets offer certainty in a consistently evolving biologics market dominated by uncertain patent scope and claim protection.

Trade secrets include “any information that can be used in the operation of a business or other enterprise,” in which such knowledge is “sufficiently valuable and secret to afford an actual or potential economic advantage over others.”¹⁸³ Such value of trade secrets in biologics applications applies to manufacturing processes, which “may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.”¹⁸⁴ However, the most important aspect of trade secrecy is that the secret actually remains a secret; without secrecy the applicant’s rights would “evaporate.”¹⁸⁵

Trade secret policy is premised on the applicant’s due diligence in determining the degree of economic value received from a trade secret’s

181. Merges & Nelson, *supra* note 7, at 854.

182. *Id.*

183. RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 (AM. LAW INST. 1995); Epstein, *supra* note 94, at 289, 301, 307; *see also* Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1003–04 (1984) (asserting that safety and effectiveness data submitted by Monsanto to the Environmental Protection Agency was a property interest cognizable by the Takings Clause insofar as the information was protected by the laws of Missouri as a trade secret).

184. 21 C.F.R. § 20.61(a) (2016); *see also* UNIF. TRADE SECRETS ACT § 1(4) (UNIF. LAW COMM’N 1979) (amended 1985) (defining a trade secret as any information that derives actual or potential economic value from “not being readily ascertainable” and that is “the subject of [measures] reasonable under the circumstances to maintain its secrecy”); Epstein, *supra* note 94, at 289 (providing additional definitions for “trade secret” from the Third Restatement of Unfair Competition and the First Restatement of Torts).

185. Love & Seaman, *supra* note 170, at 3.

competitive edge.¹⁸⁶ Simultaneously, this due diligence dissolves any Takings Clause concerns.¹⁸⁷ Takings concerns are built into the Federal Trade Secrets Act, which effectively prevents FDA regulators from “disclosing ‘any information’ that relates to ‘trade secrets, processes, operations, style of work, or apparatus’ if the information was obtained” as part of the operation of the regulators’ job.¹⁸⁸

The FDA takes a broad stance in defining manufacturing processes and designs for trade secrecy purposes.¹⁸⁹ There can feasibly be a *per se* taking of a manufacturing process—whether it is a patent or trade secret.¹⁹⁰ However, *per se* takings issues premised on any type of notice provided in legislation will dissolve these claims as the government is providing compensation in the form of market exclusivity and patent exclusivity rights.

Lastly, the Leahy-Smith America Invents Act (“AIA”) of 2011¹⁹¹ plays an important role in the decision making process for applicants.¹⁹² Not only do biologics and biosimilars applications require a certain threshold of safety and efficacy data, but patent applications also require a minimum level of disclosure.¹⁹³ The disclosure process during patent application approval and the patent dance (an infringement or invalidity assertion) includes providing an application with the “best mode” when *reduced to practice* and an inter partes review proceeding to

186. An inventor’s choice of trade secrecy illustrates her belief that research costs can be recouped without the advantages and drawbacks of patent exclusivity. Anderson, *supra* note 167, at 938.

187. See Epstein, *supra* note 94, at 324.

188. *Id.* at 289.

189. *Id.* at 290.

190. See *id.* at 299 (explaining that a *per se* taking of intellectual property does not require “physical dispossession”).

191. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

192. See generally Love & Seaman, *supra* note 170, at 3–4 (asserting that the America Invents Act (AIA) has blurred the dividing line between patents and trade secrets because the validity of patents no longer hinges on whether an applicant discloses the best mode).

193. *Id.* at 5; see also Stanley S. Wang & John J. Smith, *Potential Legal Barriers to Increasing CMS/FDA Collaboration: The Law of Trade Secrets and Related Considerations*, 58 FOOD & DRUG L.J. 613, 617 (2003) (stating that “a marketing application’s contents is governed by . . . 21 C.F.R. part 20, reflecting agency policy to[] ‘make the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade secrets and confidential commercial or financial information, and the need for the agency to promote frank internal policy deliberations and to pursue its regulatory activities without disruption’” (quoting 21 C.F.R. § 20.20(a) (2016))).

determine directly whether the parties assert infringement.¹⁹⁴ Thus, the AIA is generally known to aid with establishing broad prior user rights through disclosure requirements, thereby implicating trade-secrecy valuations for originators and applicants.¹⁹⁵

Due to the dramatic increase in litigation since the AIA's implementation caused by patent trolls,¹⁹⁶ the Innovation Act¹⁹⁷ was introduced on October 23, 2013. Even though the Innovation Act has not been approved, the underlying contention is that discovery procedures and claim construction play a critical role in abating the impact of patent trolls.¹⁹⁸ Still, these protections are not enough, and the rise in litigation will "increase the level of investment and risk associated with enforcing patent rights," further pushing biologics manufacturers towards trade secrecy protection.¹⁹⁹ The increase in costs from pre-suit investigations and "loser pays"²⁰⁰ systems may ultimately

194. See Love & Seaman, *supra* note 170, at 13; *supra* note 180.

195. See *Helsinn Healthcare S.A. v. Dr. Reddy's Labs. Ltd.*, No. 11-3962, 2016 WL 832089 (D.N.J. Mar. 3, 2106) (holding that the inventors' non-informing exploitation of the invention was not patent defeating prior art). Parties that exploit secret inventions may continue their use even after a third-party patents the same invention; before the AIA, the first inventor could have been sued by a second who happened to be first to patent. See Love & Seaman, *supra* note 170, at 15 ("[T]he AIA's expansion of prior user rights considerably reduces the risks associated with protecting preferred embodiments as trade secrets.").

196. Elizabeth J. Murphy, *H.R. 3309, The Innovation Act*, FROMMER LAWRENCE & HAUG LLP (Dec. 6, 2013), <http://www.flhlaw.com/insights/Detail.aspx?news=3f5f0d02-4972-42df-b411-263ae1b72fa4&>. Patent trolls, also known "as non-practicing entities, patent assertion entities, and patent monetizers," are beginning to infiltrate non-core or auxiliary patents—such as manufacturing processes—due to the complex nature of life sciences patents and litigations. Feldman & Price, *supra* note 103, at 773–75, 777, 781. Patent trolls use patents as bargaining chips to charge exorbitant fees to companies that seek to buy a license to practice a patent. For Unified Patents' statistical analysis of patent quality and high risk troll activity zones, see *Transactions*, UNIFIED PATS., <https://www.unifiedpatents.com/transactions> (last visited Feb. 5, 2017).

197. H.R. 3309, 113th Cong. (2013).

198. Murphy, *supra* note 196 (explaining that the Innovation Act would have heightened pleading requirements, shifted fees, limited discovery before claim construction, and established patent ownership transparency in order to place a higher burden on these trolls).

199. *Id.*

200. *Id.* (explaining that "loser pays" means that "the nonprevailing party pays reasonable fees and costs unless its position and conduct is... 'reasonably justified'").

discourage patentees from seeking to protect their rights as eagerly.²⁰¹ Generally though, the Innovation Act drives toward transparency in return for increased disclosure by—and protection of—patentees.²⁰²

IV. CURRENT STATE AND THE IDEAL STATE OF INNOVATION IN BIOLOGICAL PRODUCTS

Biologics manufacturers value their manufacturing processes and determine whether protection and exclusivity grants are more certain and more valuable than trade secrecy. The recent decision in *Amgen Inc. v. Apotex Inc.* held that the biosimilars' notice of commercial marketing is required regardless of whether the applicant partook in a patent dance.²⁰³ Additionally, the decision in *Amgen Inc. v. Hospira, Inc.*²⁰⁴ prevented Amgen from obtaining manufacturing information from Hospira deemed non-relevant to the patents-in-suit. Lastly, the U.S. Supreme Court will review the Federal Circuit's decision in *Amgen Inc. v. Sandoz Inc.*²⁰⁵ and assess whether the biosimilar maker must provide advance notice of marketing—essentially influencing whether the RPS will reap an additional six-month exclusivity period post-aBLA approval—and whether the applicant must participate in the patent dance with the RPS.²⁰⁶ The decision will not only impact the type and degree of manufacturing information exchanged between applicant and sponsor, but it will also affect how quickly consumers will be able

201. *Id.* (declaring that the Innovation Act “also provides grounds for an alleged infringer to challenge the sufficiency of initial pleadings before engaging in the merits of the case”).

202. *See id.* (recognizing that the Innovation Act “mandates an ‘ongoing’ duty to disclose patent ownership information . . . within 90 days” of any update, and that “[f]ailure to comply” with the mandate may result in fees, expenses, and damages).

203. *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1054 (Fed. Cir. 2016), *cert. denied*, No. 16-332, 2016 WL 4944497 (U.S. Dec. 12, 2016). A notice of commercial marketing informs the RPS that their customer market will soon be undercut. To adapt, the RPS will need to sell its drug at a lower price or explain to its consumers why its product is worth a higher price than its competitor's, such as a better manufacturing process. Because a biosimilars manufacturer does not have to provide the notice to the RPS until *after* market approval, the RPS should have this information readily available to adapt prior to the end of its market exclusivity.

204. No. 15-839-RGA, 2016 WL 7013483 (D. Del. Nov. 30, 2016), *appeal filed*, 16-2179 (Fed. Cir. Oct. 25, 2016).

205. 794 F.3d 1347 (Fed. Cir. 2015), *cert. granted*, 84 U.S.L.W. 3549 (U.S. Jan. 13, 2017) (Nos. 15-1039, 15-1195).

206. U.S. SUPREME COURT, 15-1039 SANDOZ INC. V. AMGEN INC.: QUESTION PRESENTED, <https://www.supremecourt.gov/qp/15-01039qp.pdf> (last visited Feb. 5, 2017).

to purchase cheaper biosimilars.²⁰⁷ These judicial decisions not only illustrate the value applicants place on exclusivity grant durations and their underlying manufacturing processes,²⁰⁸ but they also provide bases for interpreting regulatory provisions and conducting ROI calculations. Based upon current judicial²⁰⁹ and legislative trends as well as consumer demand, data exclusivity valuations have encouraged investment into FOBs as opposed to novel, less lucrative, and highly specialized disease treatments.²¹⁰

A. *Shape-up or Shake-up from Judicial Decisions: Enhancing the Value of Exclusivity*

Even though judicial decisions do not directly address whether market or data exclusivity periods provide a proper degree of incentive to innovate biologics manufacturing processes, these decisions influence whether pioneers and subsequent innovators seek those exclusivities. In the last three decades, courts have shaped these incentives in the biologics market.²¹¹ For instance, in *Scripps Clinic & Research Foundation v. Genentech, Inc.*,²¹² the Northern District of California held that Scripps, a nonprofit research organization, did not disclose the purification method that embodied the best mode at the time the application was submitted.²¹³ A robust disclosure of the scientific methodology reinforces applicants', as well as pioneers', ability to predict potential claims of subsequent innovators, and their use of process terms inherently limits the scope of product-by-process

207. Jeff Overley, *High Court Takes up Amgen-Sandoz Biosimilar Brawl*, LAW360 (Jan. 13, 2017, 2:53 PM), <https://www.law360.com/articles/792493/high-court-takes-up-amgen-sandoz-biosimilar-brawl>.

208. See Woodage, *supra* note 39, at 16 (explaining that applicants have to “thread [a] needle” by using manufacturing processes different enough not to infringe, yet similar enough to meet biosimilarity standards).

209. As of October 2016, there were five ongoing biologic/biosimilar lawsuits, in addition to *Amgen v. Apotex* (Neulasta/pegfilgrastim), *Amgen v. Hospira* (Epogen/epoetin alfa), and *Amgen v. Sandoz* (Neupogen/filgrastim). Aron Fischer, *Biosimilar Litigation Update*, BIOLOGICS BLOG (Oct. 25, 2016), <http://www.biologicsblog.com/blog/biosimilar-litigation-update>.

210. Sorscher, *supra* note 17, at 303.

211. See *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1298–1300, 1302, 1305 (2012) (illustrating patent protection as a “two edged sword,” potentially “tie[ing] up too much future use” and therefore requiring claims to possess a degree of specificity and enhancement relevant to the pertinent scientific community).

212. 707 F. Supp. 1547 (N.D. Cal. 1989), *rev'd*, 927 F.2d 1565 (Fed. Cir. 1991), *overruled by* *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009) (en banc).

213. *Id.* at 1554–55.

claims. The first Federal Circuit court ruling in *Scripps* explained that “claims are construed independent of the accused product, in light of the specification, the prosecution history, and the prior art.”²¹⁴ Thus, by limiting the scope of the claims to specific manufacturing processes, applicants are able to ensure noninfringement by engineering around a pioneer’s best mode at the time their application was filed.²¹⁵ Similarly, the Federal Circuit in *Atlantic Thermoplastics Co. v. Faytex Corp.*²¹⁶ held that if an accused infringer of a composition claim with a process limitation can show that the product was made by a different process, then there can be no warranted finding of infringement.²¹⁷ Interpreting the *Atlantic Thermoplastics* and *Scripps* decisions in tandem, “infringement requires the presence of every claim limitation or its equivalent,” otherwise the limitation does not read on the claim and subsequent innovators have freedom to operate.²¹⁸

The claim limitation concept is directly applicable to biologics innovators attempting to assert subservient patents against an RPS’s dominant patent. The RPS may attempt to create early, broad patents, which would disincentivize FOB manufacturers and subsequent pioneers’ process refinement assessments. However, the *Atlantic Thermoplastics* and *Scripps* decisions incentivize research in new and creative modes of manufacturing the same biological product with alternative manufacturing processes, or different biological products with similar claims but non-equivalent limitations. As biologics quantification methodology improves, pioneers will carve out highly refined composition claims of their own, enhancing discernibility of infringing claims. Ultimately, increased competition will ensure that the best manufacturing processes dominate the market.

214. *Scripps*, 927 F.2d at 1580. If the patent claims are “granted on the product, rather than the process for making it, subsequent process research by others will be discouraged.” Merges & Nelson, *supra* note 7, at 904.

215. Even though equivalency in manufacturing process is measured at the time of infringement, validity—the claim scope embodied in § 112’s requirements—is measured at the time of filing.

216. 970 F.2d 834 (Fed. Cir. 1992).

217. *Id.* at 846–47.

218. *Id.* at 846. *Compare Scripps*, 927 F.2d at 1583 (emphasizing that the product of a product-by-process claim is not limited by the process steps recited in the claim for purposes of analyzing alleged infringement), *with Atl. Thermoplastics*, 970 F.2d at 846–47 (articulating that process limitations in a product-by-process claim cannot be ignored when evaluating alleged infringement).

The Federal Circuit has also made strides towards reinforcing process innovation. In *Abbott Laboratories v. Sandoz, Inc.*,²¹⁹ for example, the Federal Circuit explicitly overruled *Scripps* and adopted the rule from *Atlantic Thermoplastics*.²²⁰ The Federal Circuit in *Abbott* held that process limitations in product-by-process claims are as effective as limitations in an infringement analysis.²²¹ Therefore, a biologics manufacturer claiming a process for making a biopharmaceutical compound can protect the process from infringement, even when a different pharmaceutical is produced by the process. And in *Sitrick v. Dreamworks, LLC*,²²² the Federal Circuit was concerned with composition claims whose properties or structures are highly process- or source-dependent,²²³ a concept vitally important to biologics manufacturers. Because § 112 requires one skilled in the art to practice “the full scope of the claimed invention,”²²⁴ reproducibility within the scientific and manufacturing communities requires operating and verifying the process or source limitations, without undue experimentation.²²⁵ Ultimately, the Federal Circuit held that the patentee’s broad claim language surpassed the teachings—or scope of enablement—within the patent specification, and the claims were therefore non-commensurate with the enrichment of public knowledge.²²⁶

219. 566 F.3d 1282 (Fed. Cir. 2009) (en banc).

220. *Id.* at 1291, 1293.

221. *Id.* at 1293–95.

222. 516 F.3d 993 (Fed. Cir. 2008).

223. *See id.* at 995–96 (discussing a dispute over video game versus movie technology).

224. *Id.* at 1000.

225. Karshedt, *supra* note 162, at 116, 155.

226. *Sitrick*, 516 F.3d at 999 (citing *Auto. Techs. Int’l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007)). In U.S. patent law, claims define the scope of legal protection that the federal government grants to the owner or exclusive licensee of a patent. *See* 35 U.S.C. § 112 (2012) (establishing that a patent application shall include “one or more claims particularly pointing out and distinctly claiming . . . the invention”); *see also* § 154(a) (addressing the rights of a patent owner or licensee, the patent term, and the content of a patent). But when construed in view of the recent *Phillips* decision, “claim construction [can] result in a narrower claim scope.” Bryan J. Braunel, *USPTO Amends AIA Rules*, FROMMER LAWRENCE & HAUG LLP (May 3, 2016), <http://www.flhlaw.com/USPTO-Amends-AIA-Rules-05-03-2016>. Similarly, the Supreme Court in *Association for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107 (2013), was particularly interested in retaining sufficient incentives for biotech firms to ensure future innovation is not inhibited. *Id.* at 2116 (addressing patent breadth with respect to DNA, which is best described by its structure rather than by function). After all, “too broad an interpretation of this exclusionary principle” will limit incentive to protect novel, societally beneficial

The Senate's unanimous approval of the Defend Trade Secrets Act (DTSA)²²⁷ on April 4, 2016, should reinforce the security of innovators' property rights.²²⁸ Creating a baseline for enabled disclosure while reinforcing trade secret viability ensures innovators focus their time and monetary investments towards holes in prior art; thus, increasing the value of enabled innovation.

The Federal Circuit recognizes that biological product applications have interrelated claims—source, composition, and process claims may all be part of an applicant's claimed biopharmaceutical.²²⁹ Biologics manufacturers see the capabilities that biologics licenses provide, yet they strategically navigate the statutory and regulatory framework to minimize scientific knowledge disclosure.²³⁰ *Sitrick* exemplifies how the Federal Circuit requires essential, reproducible knowledge for enablement in an application, knowing those same claims may be used to limit competition in the future.²³¹

Still, the Supreme Court's *FTC v. Actavis, Inc.*²³² and Third Circuit's *Mylan Pharmaceuticals v. Warner Chilcott*²³³ decisions have cast a shadow over the biologics market, potentially affecting an alleged infringer's ability to receive payment in return for staying off the market for a specific period.²³⁴ At issue in both cases was whether a viable antitrust challenge may be claimed against a pay-for-delay, or reverse-payment settlement, scheme. Essentially, the underlying actions at issue involved "product hopping," whereby insignificant modifications are made to the

inventions that all, to some degree, "embody, use, reflect, rest upon, or apply laws of nature natural phenomena, or abstract ideas." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012).

227. Pub. L. No. 114-529 (2016).

228. Jessica L. Sblendorio, *The Defend Trade Secrets Act: A Remedy Background and Implementation*, FROMMER LAWRENCE & HAUG LLP (Apr. 28, 2016), <http://www.flhlaw.com/DefendTradeSecrets>.

229. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1358–68 (Fed. Cir. 2009).

230. Minimizing patent and regulatory disclosure reinforces licensing schemes, such that licensees must purchase competitor's materials in order to feasibly manufacture and commercialize the biologic independently. Dan L. Burk, *Misappropriation of Trade Secrets in Biotechnology Licensing*, 4 ALB. L.J. SCI. & TECH. 121, 140 (1994). In the biologics manufacturing industry, inventors would retain "essential know-how" through secrecy while obtaining patent protection with strategic disclosure. Anderson, *supra* note 167, at 941.

231. *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999, 1000 (Fed. Cir. 2008).

232. 133 S. Ct. 2223 (2013).

233. 838 F.3d 421 (3d Cir. 2016).

234. Tucker & Wells, *supra* note 39, at 102. See generally Joshua B. Fischman, *The Circular Logic of Actavis*, 66 AM. U. L. REV. 91 (2016).

pioneer drug, extending the drug's exclusivity, thereby forcing subsequent generic competitors off the market and requiring they restart the regulatory process.²³⁵ Relevant to the biologics industry are the outer edges of these decisions, which required applicants to come to the table with product reformulations that provide patient benefits.²³⁶ Once patient benefits are proven to the reference product manufacturer, these case decisions provide reason to believe that any reverse-payment settlements would be permitted as an economically efficient means to resolve infringement litigation.²³⁷ Thus, societal health impact is an inherent consideration and bar that innovators must surmount to justify their reasonable, investment-backed expectations.

Lastly, *Amgen Inc. v. Sandoz Inc.* was the first Federal Circuit decision to substantively interpret the BPCIA.²³⁸ The Supreme Court's decision to review the Federal Circuit's ruling "will have a significant economic impact on both reference product sponsors and biosimilar applicants."²³⁹ The *Amgen* decision from 2015 held that (1) a biosimilar applicant is not required to participate in the patent exchange procedure outlined within section 351(I) of the PHSA, and (2) a biosimilar applicant *must* provide the reference product sponsor with 180 days' notice of commercial marketing only *after* the FDA approves the biosimilar application.²⁴⁰

Nevertheless, biosimilar applicants may currently choose to not participate in the patent exchange process.²⁴¹ Even though the Federal Circuit holding gives a biosimilar applicant more control over patent disclosure and litigation processes, the RPS will not have the benefit of the patent exchange procedure to determine similarity to an FOB and its manufacturing processes, making it more difficult for the RPS to meet heightened pleading requirements.²⁴²

235. *Mylan*, 838 F.3d at 426; *see also* Mark S. Levy, *Big Pharma Monopoly: Why Consumers Keep Landing on "Park Place" and How the Game Is Rigged*, 66 AM. U. L. REV. 247, 276–79 (2016) (defining product hopping's roll in anticompetitive schemes carried out by pharmaceutical companies).

236. Tucker & Wells, *supra* note 39, at 104.

237. *Id.* at 103.

238. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347, 1351–62 (Fed. Cir. 2015), *cert. granted*, 84 U.S.L.W. 3549 (U.S. Jan. 13, 2017) (Nos. 15-1039, 15-1195).

239. Colletti & Worley, *supra* note 145.

240. *Amgen*, 794 F.3d 1356–58, 1360; *see also* Colletti & Worley, *supra* note 145.

241. Colletti & Worley, *supra* note 145.

242. *Id.* ("[Section] 351(I)(9)(C) does not adequately address a reference product sponsor's needs because it is only directed to composition and method of use claims and not manufacturing and process claims."); *see also* Courtenay C. Brinckerhoff,

B. Incentivizing High-Quality Innovation for Biologics Manufacturers

The biologics regulatory pathway must enable biologics manufacturers to respond quickly to scientific and technological growth. A biopharmaceutical market that constantly reassesses and protects innovation will incentivize manufacturers to disclose new manufacturing process knowledge in return for grants of exclusivity.²⁴³ Innovation reflects a stronger grasp of process knowledge. Manufacturers typically innovate upon prior art and patent novel processes when the short-term sacrifice is worth the long-term return.²⁴⁴ Biosimilars innovation takes the forms of “enhanced overall design,”²⁴⁵ new therapeutic uses for approved drugs,²⁴⁶ and lower costs for consumers. Cumulative innovation is particularly applicable to biologics and biosimilars manufacturing processes during the current rapid growth of the biosimilars market.²⁴⁷ Cumulative innovation includes better processes for manufacturing a similar drug²⁴⁸ and safer, more efficacious drugs from more controlled manufacturing processes.²⁴⁹

AbbVie Sues Amgen on 10 of 100 Humira Patents (Aug. 9, 2016), <https://www.foley.com/abbvie-sues-amgen-on-10-of-100-humira-patents-08-09-2016> (showing that leading the first round of the patent dance enables the biosimilar applicant to strategically target weaker RPS claims).

243. Cf. Jennifer L. Bachorik & Courtenay C. Brinckerhoff, *USPTO Launches Patents 4 Patients*, FOLEY & LARDNER LLP (Aug. 2, 2016), <https://www.foley.com/uspto-launches-patents-4-patients-08-02-2016> (illustrating that frequent disclosure opportunities and constant incentive to innovate may be more important than an expedited approval process).

244. See Merges & Nelson, *supra* note 7, at 878 (emphasis omitted) (assuming innovation responds quickly to market demands and introduces consumers to new improvements).

245. See *id.* at 859.

246. See *id.* at 883. But see W. Nicholson Price II & Timo Minssen, *Will Clinical Trial Data Disclosure Reduce Incentives to Develop New Uses of Drugs?*, 33 NATURE BIOTECHNOLOGY 685, 685 (2015) (revealing that not all new uses for approved or patented drugs are patentable).

247. Merges & Nelson, *supra* note 7, at 898. The capacity and opportunity to innovate increases as the industry develops new drugs and prepares for the development of future therapeutic uses. See Price, *Innovation Policy Failures*, *supra* note 8, at 346. For a discussion of why prospective patenting is of particular relevance where there is a continuum—or series—of opportunities to develop the commercialization of biologics while responding to market demands, see generally Nithya Anand, *Accommodating Long Term Scientific Progress: Patent Prospects in the Pharmaceutical Industry*, 16 J. INTELL. PROP. RTS. 17 (2010).

248. Huzair & Kale, *supra* note 38, at 251.

249. *Id.*

Quality, on the other hand, creates a scale to measure innovation. Quality assessments typically require comparative analyses but also require fiscal justification for enhanced process control, and new product formulation and design.²⁵⁰ These regulation-mandated quality assessments are important because, from the viewpoint of a market consumer, quality is hard to observe.²⁵¹ Once a drug is approved for sale in commerce, the regulatory structure has difficulty “detect[ing] quality problems and impos[ing] restrained response[s].”²⁵²

High-quality innovation stems from information sharing.²⁵³ Just as there are degrees of information sharing,²⁵⁴ there are degrees of quality, and the incentive structure must account for these varying innovation levels and their impact on societal health.²⁵⁵ Clinical superiority, required by the Orphan Drug Act regulations, is demonstrated by therapeutic advantages from clinical trials or major contributions to patient care.²⁵⁶ The current four- and twelve-year regimented structures do not keep pace with science; biologics manufacturing processes drift with time, and if a manufacturer can obtain more process control, then it should not feel restricted to wait until their exclusivity period lapses. Altering manufacturing processes in pursuit of clinically superior biologics will occur in a less regimented exclusivity structure. Therapeutically advantageous products, in return for regulatory

250. Price, *Making Do in Making Drugs*, *supra* note 103, at 559.

251. *See id.* at 558–59 n.429 (noting that particularly for sterile injectable drugs, consumers already have compromised immune systems, making differentiation between drug contamination and infection difficult).

252. *Id.* at 559. For an illustrative example of systemic quality issues from one of the United States’ largest sterile, injectable drug manufacturers, Hospira, see Zachary Brennan, *Slew of Recalls, Form 483 Shake Hospira*, IN-PHARMA TECHNOLOGIST (Mar. 9, 2015) <http://www.in-pharmatechnologist.com/Regulatory-Safety/Slew-of-recalls-Form-483-shake-Hospira>.

253. *See* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1030 (2016) [hereinafter *Manufacturing Barriers*].

254. *Id.* at 1030, 1045 (stating that sharing information has advantages from both patent and trade secrecy law: publishing fundamental knowledge about biologics manufacturing processes through patent law, while fostering licensing through trade secrecy). Similarly, reverse-engineering can explore alternative methodology, which ultimately may be cost-effective or therapeutically superior. *Id.* at 1049.

255. *See* Stroud, *supra* note 88, at 638 (advocating for degrees of regulator stringency, or a sliding scale, depending upon a biologics product classification system).

256. 21 C.F.R. § 316.3(b)(3) (2015); *see* Dudzinski, *supra* note 75, at 201. By creating an alternative orphan drug regulatory pathway, the legislature recognizes varying degrees of quality and the importance of incentivizing hard-to-manufacture drugs.

certainty and efficiency, provide manufacturers with the incentive to invest in therapeutically advantageous processes.

C. Incentivizing Biologicals Manufacturers with an Exclusivity Tier System

The pharmaceutical industry, compared to other industries like hi-tech, spends much more on R&D but with intimidating rates of failure.²⁵⁷ To overcome these high barriers to entry, biologics and biosimilars manufacturers must have the fiscal incentive to innovate and the knowledge that new, proven manufacturing achievements will provide additional ROI. Currently, the FDA rarely grants market exclusivity privileges for manufacturing process improvements alone; hence, manufacturing processes—or at least large portions thereof—are typically withheld as trade secrets or strategically claimed within companion composition claims.²⁵⁸ As a result, significant opportunity exists in regulatory framework to incentivize R&D of biologics manufacturing processes. After all, every biopharmaceutical compound is not created equal, so why should their exclusivity grant durations all be equal?

Innovation saves both patients and insurance companies from substantial cost while reducing governmental healthcare expenditures.²⁵⁹ Just as legislatures reinforce collaborative drug development research, they also should reinforce research, development, and implementation of collaborative innovative manufacturing methodology—especially with respect to biopharmaceuticals, which provide large societal health implications. Legislatures could directly reinforce collaboration by providing incentives to adhere to a more robust biologic disclosure system.²⁶⁰ Even though longstanding executive branch policies have impaired politically-

257. Price, *Making Do in Making Drugs*, *supra* note 103, at 785.

258. *Id.* at 523.

259. See Price, *Innovation Policy Failures*, *supra* note 8, at 343 (“[E]xpenditures on drugs make up over [fifteen] percent of health care costs . . . ; see also *id.* at 346 (estimating that reducing manufacturing inefficiency could save fifteen to ninety billion dollars annually worldwide; in the United States, that could result in consumer surplus gains of \$47.4 billion annually or increased R&D health gains worth \$574 billion annually).

260. Tucker & Wells, *supra* note 39, at 101 (“The BPCIA contains a number of exclusivity provisions designed to reward innovation in developing biologics and encourage future research and development; see Price, *Making Do in Making Drugs*, *supra* note 103, at 497, 509 (asserting that “calibrated policy successfully drives innovation in drug discovery and development, but not in drug manufacturing,” which is why disclosure and discourse must be economically incentivized).

driven innovation,²⁶¹ the Obama Administration has recently emphasized that when the government is needed to “help spur technological advances and broaden technology adoption . . . the Federal Government can help catalyze advances, promote market-based innovation, and encourage more competitive market outcomes.”²⁶²

Disclosure axiomatically drives innovation.²⁶³ All designs—not just follow-ons and biobetters—use some sort of prior art discourse to their advantage combined with their own innovative capabilities. A robust disclosure-incentive system revolves around the four- and twelve-year exclusivity provisions outlined in the BPCIA.²⁶⁴ Essentially, the sponsor will disclose the minimum information necessary to enable someone skilled in the art to understand the novelty of the biological manufacturing processes. Thus, disclosure during the patent filing and protection process is the rate-determining step for innovation built upon prior art.

However, trade secrecy provides value through predictability and should not be abandoned completely for increased discourse.²⁶⁵ Trade secret protection is a compromise with the legislature on which the four- and twelve-year exclusivity valuations are built: originators will disclose only what the government can economically entice the originator to

261. Merges & Nelson, *supra* note 7, at 840, 842.

262. Price & Rai, *supra* note 253, at 1059 (quoting 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), <http://www.iccsafe.org/gr/Documents/AdoptionToolkit/FedStandardsMemo-011712.pdf> (identifying health-care technology as a national priority)).

263. Price & Rai, *supra* note 42, at 189.

264. Tucker & Wells, *supra* note 39, at 101 (“The BPCIA restricts a follow-on manufacturer from filing an application until four years after approval of the reference biologic . . . [and] further provides the reference manufacturer with a 12-year [market] exclusivity period, during which the FDA cannot approve an FOB relying on the innovator’s prior showing of safety, purity, and potency for approval.”).

265. See Love & Seaman, *supra* note 170, at 14 n.65 (reinforcing use of the prior user defense, such that trade secrecy provides a limited window of enforceable rights, prior to patenting). Section 112 of the Patent Act requires “[t]he specification shall 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, or with which it is most nearly connected, to make and use the same” 35 U.S.C. § 112(a) (2012). Otherwise, non-enabling disclosures are of very little value to the public and do not allow researchers to verify whether the product is identical to the originator; see also Price, *Innovation Policy Failures*, *supra* note 8, at 351 (explaining that “trade secrecy creates incentives for innovation by keeping others from copying the innovation and therefore allow[s] supracompetitive pricing”).

disclose. Just as there is no Takings Clause issue when legislation provides notice of the required patent dance and aBLA application criteria, the government must allow originators to withhold certain trade secrets when it is a viable and legitimate business option.²⁶⁶

Holistically, innovation through disclosure occurs by one of three methods: (1) mandating disclosure, (2) incentivizing disclosure/disclosure through market exclusivity periods, or (3) letting applicants meet bare minimum requirements from USPTO and aBLA statutory standards. The manner in which these methods impact society²⁶⁷ and how the impact can be tailored through the FDA's grant of market exclusivity are examined below.

1. *Incentive scheme must be capable of responding to scientific improvements*

For the biologics and biosimilars market to gain acceptance and accelerate market growth of biopharmaceuticals—bolstering investments and innovation within the field—the public must view these therapies as safer and of higher quality.²⁶⁸ Biopharmaceuticals have the opportunity to be a therapeutically superior product relative to small-molecule drugs.²⁶⁹ Viewing these medications as superior²⁷⁰ and worth consumers' financial investments makes sense, but with so much money at stake, it also requires transparency.²⁷¹ Patients, driven by market

266. However, it is critical to recognize the trade-off: the rights and protections provided by patents in return for enabled disclosure.

267. Price, *Regulating Secrecy*, *supra* note 33, at 1775.

268. See *supra* text accompanying notes 74–81.

269. See Tkaczuk & Jacobs, *supra* note 56, at 3, 6 (discussing that “[g]uidance documents and position statements from established societies worldwide have the potential to help clinicians, payers, and providers understand” and inform patients of biological and biosimilar product treatments).

270. The sole purpose of these clinical trials should be proving superiority. Dranitsaris et al., *supra* note 49, at 482 (stating that designing current clinical trials revolves around equivalence; in an equivalence trial, neither superiority nor inferiority can be tested).

271. Overall, consumer and physician decisions, in conjunction with organizations like ExpressScripts, inherently consider clinical trials and the transparency of trial requirements and results. See, e.g., *id.* at 483 (asserting that non-inferiority trials are useful for assessing further product investments, because they test whether the new treatment is at least non-inferior to the control, and if it is, the superiority hypothesis—which attempts to determine if the experimental group is better than the control—can be evaluated). “[N]on-inferiority trials are efficient because a definitive conclusion can be made about a new drug from a single randomized trial,” enabling manufacturers to facilitate product investment decisions and translate the underlying value of these decisions to consumers, thereby justifying product pricing with respect to safety, efficacy, and purity. *Id.*

forces, will seek to determine (with their physicians) which medications are cost-effective. Safety and efficacy transparency will enhance public health by improving informed health decision making. Furthermore, the public's trust in regulatory oversight and the pharmaceutical market will help drive large cross-border clinical trials for rare diseases, adding opportunities for innovation and market approval.²⁷²

Market acceptance requires an equity analysis because of disclosure. Pioneers must enjoy a level of reassurance that disclosure will not impede their ability to recoup an initial investment.²⁷³ Patent scope requirements²⁷⁴ consider and balance these trade-offs for BLAs and aBLAs.²⁷⁵ Striking the right balance between disclosure and patent scope will ultimately drive biologics research, and a tiered system is a step in the right direction.²⁷⁶

Lastly, the scientific state of biologics and their manufacturing processes develop at an alarmingly quick rate.²⁷⁷ Clearly, natural

272. Price & Minssen, *supra* note 246, at 685.

273. A pioneer would likely need to go beyond a demonstration of “substantial equivalence” to win over consumers in a way that would allow them to recover their investment. See Wang & Smith, *supra* note 193, at 616 (“[A] determination of ‘substantial equivalence’ may involve data that falls far short of the clinical testing or experience often required to demonstrate [a] health benefit to the satisfaction of CMS . . .”). When assessing Medicare coverage of new products or services, there is a required “reasonable and necessary” assessment of the new diagnosis or treatment. 42 U.S.C. § 1395y(a) (2012). If substantial equivalence data fall short of being reasonable and necessary, then investments will be for naught.

274. See David J. Kappos & Stuart Graham, *The Case for Standard Measures of Patent Quality*, 53 MIT SLOAN MGMT. REV. 19, 19 (2012) [hereinafter *Standard Measures of Patent Quality*] (explaining that a patent application involves “a series of claims that attempts to describe new and nonobvious processes, machines, manufacturing methods or composition of matter” and that “quality” and therefore patent specifications and descriptions are the top priority of every patent office).

275. The patent versus trade secrecy dilemma reflects the highly scientific character of the biologics industry. Systemic problems of innovation and competition need to be considered and addressed by innovators during their decision-making process.

276. Merges & Nelson, *supra* note 7, at 843.

277. Inevitably, more manufacturers will assess whether they can meet biosimilarity standards before designing a pioneer drug trial; thus, the scientific state of methodology for determining biosimilarity will most likely impact the speed at which biologics science develops. See Strand & Cronstein, *supra* note 36, at 221 (examining amino acid composition, terminal amino acid sequence of protein/peptide, presence of disulfide bonds, sulfhydryl groups glycosylation, protein folding, and some higher order structure profiles; because these tests examine acceptable batch-to-batch variation, they will need to be employed and advanced in every manufacturing setting, at every production run).

“drift” of manufacturing processes allows sponsors to explore additional novel claims; however, innovators must value these claims and pursue protection or exclusivity in accordance with their impact to societal health.²⁷⁸ Still, biologics manufacturers possess a consistent fear of reverse-engineering, which continues to plague the patent landscape.²⁷⁹ As scientific knowledge of biologics and their manufacturing processes increase, the cost of independently discovering or reverse-engineering originator manufacturing designs will diminish.²⁸⁰ Superior analytical techniques will establish a stronger conceptual base of knowledge. Improved analytical techniques are particularly important for biologics and biosimilars manufacturing processes because accurate measurements of process improvements allow a sponsor to quantitatively predict enhancements in the product and to societal health. Because process improvements correspond to structural differences, innovative analytical techniques will help render claimed material novel. However, innovative opportunities for biologicals manufacturing will not flourish unless the current market exclusivity incentive structure adapts.

278. See McCamish & Woollett, *supra* note 4, at 409 (determining that, because an originator product varies over its lifetime, batch-to-batch variability, a.k.a. drift-assessments, provide opportunities for innovators to test manufacturing design alterations, which can ultimately improve safety, purity, efficacy, or cost); see also Bui et al., *supra* note 34, at 5 (providing an overview of the manufacturing variability guidelines set by the International Conference on Harmonization (ICH)).

279. The law does not penalize or bar discovery of the trade secret through reverse engineering, independent laboratory research, canvassing published literature, or inadvertent disclosure by the holder. By promoting ethical behavior among competing businesses, trade secrecy prohibits and penalizes misappropriation: unauthorized disclosure or use of another’s trade secret when the information is obtained by improper means or through a breach of confidence. See *supra* Part III; see also *ILG Indus. v. Scott*, 273 N.E.2d 393, 398 (Ill. 1971) (discussing that “trade secrets can often be discovered by lawful means” and the difficulty in ascertaining whether something is a trade secret).

280. Trade secret protection can be easily lost through independent discovery, reverse engineering, or inadvertent disclosure. “Thus, inventors with discoveries that are eligible for patent protection are likely to seek such protection rather than relying on the more mercurial protection of trade secrecy.” Burk, *supra* note 230, at 127–28 (citing *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 490 (1974)); see also *supra* note 92 (explaining that improving manufacturability and prior art classification will entice inventors to apply for patents earlier in the biologics development life-cycle).

2. *Make-it or break-it with market exclusivity*

The FDA's grant of market exclusivity directly influences originators' and applicants' analysis of ROI. In return for regulator-facilitated disclosure, biologics—whether biobetter or simply novel—are provided with a twelve-year market exclusivity,²⁸¹ four years of which an innovator cannot attempt to develop upon the patented material in conjunction with RPS clinical trial data.²⁸² There are no Takings Clause concerns when notice of disclosure is accompanied by regulatory benefits.²⁸³ Thus, the BPCIA provides reasonable “investment-backed expectations,” which must be anticipated when applying for patent or biological product protection and exclusivity.²⁸⁴

Besides grants of market exclusivity in return for disclosure, patent protection provides exclusive rights, requiring significant time and money to reduce to practice. Thus, there needs to be an originator-to-innovator advantage: originators who actively innovate upon their existing patent and exclusivity grants, as opposed to originators who cling to the same manufacturing process claimed in their original application. Originators possess valuable scientific and process knowledge, which is not easily translated through applications and claimed inventions.²⁸⁵ Originators are highly capable of using their

281. Overley, *supra* note 145 (explaining that requiring biosimilar notice in all circumstances would essentially extend the twelve or twelve-and-a-half year exclusivity because it is highly unlikely a biosimilar will be licensed under the BPCIA without being officially approved for sale).

282. 42 U.S.C. § 262(k)(7)(B) (2012); *see supra* notes 87–91 and accompanying text.

283. Epstein, *supra* note 94, at 296, 313; *see also* Penn Cent. Transp. Co. v. City of New York, 438 U.S. 104, 124 (1978) (examining the character of the government action, the economic impact of the action, and whether the government action has vitiated reasonable investment-backed expectations—which is often the central focus of regulatory takings analyses); Amgen Inc. v. F. Hoffman-La Roche Ltd., 580 F.3d 1340, 1379 (Fed. Cir. 2009) (acknowledging that the structure and function of a prior art was difficult to reproduce and verify, illustrating that a change in process apparently created a different structure, rendering the claimed material novel).

284. Epstein, *supra* note 94, at 303. Validity determinations—enablement, written description, and definiteness—are measured at the time of filing, whereas equivalents are measured at the time of infringement; thus, consideration of after-arising technologies would not be considered a reasonable investment-backed decision.

285. *See Biobetters Versus Biosimilars*, *supra* note 4 (explaining that repurposing and/or streamlining an innovator's manufacturing facility to support biobetter production offers efficiency and economics of scale advantages). Similarly, because “downstream process optimization” parameters are often withheld as trade secrets, the originator possesses vital and valuable process-specific knowledge. *See* Paul A.

existing knowledge to improve upon their own claimed, prior art. Similarly, a pioneer's manufacturing process and product investment is reduced to practice when their patent provides clear, enabled descriptions—applicants rely upon the strength of previous patents to provide strong scientific knowledge to build upon.²⁸⁶ Otherwise, applicants essentially build biologics manufacturing processes from scratch, resulting in “unnecessary and wasteful duplication of creative effort.”²⁸⁷ Any “saved” money, or lower financial burden, will be directed towards developing and protecting established rights—critical to both innovators and applicants. Ultimately, there is a lower regulatory barrier to protecting improvements upon existing claims, and these companies can employ offensive strategies to protect their drug portfolio.²⁸⁸ Conservation of manufacturing process knowledge through robust disclosure systems and originator-to-innovator incentives enables the PTO to more accurately assess patent scope and strength,²⁸⁹ thus, the originator and/or applicant will enjoy an enhanced level of protection and the cycle of reinforcing innovation upon existing patent claims

Calvo, *Choosing Between Patent and Trade Secret Protection in a Biosimilar World*, BIOSIMILAR DEV. (Jan. 13, 2016), <http://www.biosimilardevelopment.com/doc/choosing-between-patent-and-trade-secret-protection-in-a-biosimilar-world-0001>.

286. See Anderson, *supra* note 167, at 966 (“[O]verall investment is reduced when patent strength is increased for inventions in which secrecy is a viable option.”); see also *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 481 (1974) (emphasizing the importance of circulating the information contained in a patent to those who are “skilled in the trade” for the public good, in order to “stimulate ideas and the eventual development of further significant advances in the art”).

287. *Standard Measures of Patent Quality*, *supra* note 274, at 20. Still, the non-rivalrous and non-excludable nature of patents allows disclosed claims to become retrofitted into new processes, thereby imperfectly—and potentially ingeniously—imitating prior art.

288. Price, *Making Do in Making Drugs*, *supra* note 103, at 527, 544 (assuming valuable or high quality by design, “public disclosure required by a patent can lower that entry barrier by providing information about both the biologic-specific manufacturing process and general manufacturing processes for biologics”). Aranesp, a biobetter of EPO, was launched prior to EPO's patent expiration, and as a result Amgen was able to maintain much of its market share after patent expiration. *Biobetters Versus Biosimilars*, *supra* note 4.

289. See *Standard Measures of Patent Quality*, *supra* note 274, at 20 (stating that an essential role of the government, with respect to supporting scientific and commercial innovation, is to properly define and enforce property rights); *id.* at 22 (searching for prior art and making novelty and obviousness determinations are the most important standards for assessing patent scope during the examination process).

would repeat. Accordingly, disclosure will simultaneously promote oversight through transparency and labor mobility.²⁹⁰

However, understanding why regulator-facilitated disclosure may not incentivize innovation ensures these limitations are mitigated through other means.²⁹¹ Originators and innovators rarely invest in new uses for their approved drug unless they can be ensured sufficient exclusivity after approval. Additionally, disclosure severely limits the patentability of new uses designed by follow-on applicants, both because of dominant patents and prior art (novelty, obviousness, and anticipation) issues. Like the originator-innovator advantage, the exclusivity scheme should provide proportionate advantages to originators of biological products in return for manufacturing innovation.

3. *Capitalizing on scientific developments requires an adaptable market exclusivity landscape*

Societal health is enhanced when patients benefit from scientifically superior medications earlier on in their treatments. Recurring opportunities for grants of data exclusivity within 42 U.S.C. § 262(k)(7)(B), subject to case-by-case extensions, will create frequent fiscally justified process reassessment schemes. Altering data exclusivity durations by applying a tiered system similarly creates a much-needed drastic change in the biologics and biosimilars patenting landscape.

Any potential solution must target lowering barriers while maintaining safety and incentivizing innovation.²⁹² Ultimately, drug development and protection costs can be lowered by combining the socially useful aspects of disclosure with the return on innovative manufacturing processes provided by secrecy. Granting one to four additional years of data exclusivity during a biologics' market exclusivity period will incentivize applicants to pursue exclusivity

290. Decreasing the importance of secrecy and associated non-disclosure and non-compete agreements promotes labor mobility. *See generally* Victor M. Harding, *Trade Secrets and the Mobile Employee*, 22 BUS. LAW. 395, 396, 407 (1967) (illustrating the axiomatic risk that employees face when working “in an area where he may make use of his former employer’s trade secrets,” especially due to the fact that “[y]ounger employees and engineers have the least sense of loyalty” and more commonly move from job-to-job in the same industry). Similarly, enhanced levels of disclosure allow industry manufacturers and physicians to police the market and assess market deficiencies or opportunities for themselves. *See supra* notes 28, 271.

291. *See generally* Price & Minssen, *supra* note 246.

292. Price, *Innovation Policy Failures*, *supra* note 8, at 352.

grants commensurate with their investment and clinical data strength.²⁹³ Every biopharmaceutical must be approved as safe and effective, but the investment and societal health impact vary with each drug. A tiered system, with application specific regulatory oversight, will properly reflect each biopharmaceutical's value with respect to societal health improvement.

Furthermore, potentially longer exclusivity periods will bolster collaboration. A collaborative R&D group would create a fast-track of biological product development,²⁹⁴ but it must consider issues involving public rights to use this knowledge.²⁹⁵ With sufficient *ex ante* incentives for members of the collaborative research group, public domain knowledge can spill over to societal health, benefitting us all.²⁹⁶

High-quality innovation also would combat previous pharmaceutical manufacturing deficiencies and ensure that the biological product market is poised for rapid innovation.²⁹⁷ High-quality innovation requires manufacturers to constantly reassess and build new continuous manufacturing, monitoring, and quality-testing

293. Correlating terms with innovative inputs and value outputs. This provides manufacturers with both more opportunity, less risk, and more predictability.

294. See Margie Patlak, *Competitors Try Collaboration to Speed Drug Development*, 102 J. NAT'L CANCER INST. 841, 842 (2010) ("[T]he increasing complexity, amount of data, and downstream effects on regulatory science is leading to the dawning realization that nobody is smarter than everybody."); Roe, *supra* note 4, at S28 (explaining that in 2011, the National Comprehensive Cancer Network formed the Biosimilars Work Group, taking a multi-professional approach to producing a consensus statement for biosimilar implementation in the clinical practice); see also Patlak, *supra*, at 841–42 (describing how Merck and AstraZeneca joined forces to test a combination treatment with two compounds, which provided a competitive advantage and enabled the product to be developed more rapidly; they shared any intellectual property resulting from collaboration but each kept the intellectual property rights to their compound).

295. Price & Minssen, *supra* note 246, at 685; see also *On Assignment: Hacking Cancer*, *supra* note 21 ("What if we had a system where all of the intellectual property could be shared amongst the scientists so the breakthrough made in one place could be used by someone in another place?" (quote appears at 8:22 in video)). The NIST initiatives to use public-private consortia to generate fundamental knowledge and place it in the public domain are likely to yield substantial benefits for both competition and innovation.

296. See Roe, *supra* note 4, at S29 (suggesting that cost-savings driven by biosimilars for supportive care will incentivize innovators to invest in treatments to manage the cancer).

297. See Price, *Innovation Policy Failures*, *supra* note 8, at 344–45 ("[M]anufacturing is largely noninnovative and relies on outdated techniques and processes."); see also *supra* note 252 and accompanying text.

into the process.²⁹⁸ Additionally, there must be low process rigidity to ensure manufacturers are incentivized to continue research and development upon prior art.²⁹⁹ Manufacturers should not feel secure when they can reap an ROI while sitting on their patent rights and exclusivity periods—a system meant to constantly build upon innovation of prior art. Constant innovation can be accomplished by creating a separate validation pathway for process improvements, requiring disclosure when firms fail to maintain manufacturing quality standards (resulting in drug shortages),³⁰⁰ and eliminating the “pay-for-delay” scenario when societal health benefits are minimal.³⁰¹ Similarly, increased regulatory flexibility should be provided to manufacturers through the BPCIA.³⁰²

Originators and innovators who have demonstrated excellence and sound manufacturing process characterization should be the first to capitalize upon exclusivity and patent protection.³⁰³ For instance, in 2010, Brazil developed a regulatory pathway dependent upon biosimilar complexity with a corresponding amount of evidence required to support efficacy and safety.³⁰⁴ Likewise, the FDA should create a tiered system; exclusivity grants should be proportional to the anticipated (and proven) societal health benefits, which may vary during an exclusivity period. This would ensure that innovators with sufficient capital are incentivized to invest additional resources where they provide the greatest value: improving prior user rights. Even if

298. Price, *Innovation Policy Failures*, *supra* note 8, at 345. “Consistent quality, smaller facilities, and reduced capital and operating costs” highlight the advantages of continuous biopharmaceutical manufacturing. *Continuous Biopharmaceutical Manufacturing: Can It Live up to the Hype?*, INT’L SOC’Y FOR PHARMACEUTICAL ENGINEERING (Jan. 4, 2017), <http://blog.ispe.org/continuous-biopharmaceutical-manufacturing-can-it-live-up-to-the-hype> (hypothesizing that a 150,000-liter fed batch capacity typically requires ten, 15,000-liter stainless steel reactors, while a continuous process could function with ten, 1000-liter reactors).

299. Price, *Innovation Policy Failures*, *supra* note 8, at 344–45. In areas of rapidly evolving science and incomplete knowledge, regulation itself must be dynamic and adaptive.

300. See Matthew DeCamp et al., *Chemotherapy Drug Shortages in Pediatric Oncology: A Consensus Statement*, 133 PEDIATRICS e716, e718 (2014).

301. Blackstone & Fuhr, *supra* note 51, at 7; see also Tucker & Wells, *supra* note 39, at 102–03 (providing an overview on reverse-payment schemes).

302. See *supra* note 20 and accompanying text.

303. See Price, *Innovation Policy Failures*, *supra* note 8, at 352–53 (modeling after the Occupational Safety and Health Administration’s Voluntary Protection Programs).

304. Tkaczuk & Jacobs, *supra* note 56, at S6 (noting that this scheme is meant to incentivize innovation and increase utilization and the market for development of biosimilars).

innovators fall short of meeting all statutory requirements for a patent or for protection under the BPCIA, proving enhanced efficacy or manufacturing efficiency must still be incentivized when the manufacturing process alteration potentially improves societal health. Tailoring rewards for both cost input and value output help properly reward and incentivize innovation.³⁰⁵ Thus, these innovators should be able to fall back on, for example, a change in dosing regimen³⁰⁶ when it allows the drug to reach more or different classes of patients and therefore supports an FDA grant of additional data exclusivity illustrating societal health enhancement.

Lastly, Congress should create a framework that mandates innovation in return for market exclusivity³⁰⁷ or continued patent validity.³⁰⁸ Because competition within the FOB market is expected to closely resemble brand-to-brand, small-molecule pharmaceutical competition, innovation may not occur as organically with new entrants in the generics market.³⁰⁹ Encouraging innovation, however, will ensure quality-by-design processes³¹⁰ and reinforce follow-on manufacturers' development of innovative analytical tools to quantitatively measure improved quality.

Ultimately the only value that matters during the patent versus trade secret decision-making process is whether the originator/applicant feels they can obtain an ROI and capture market share to set-up prospective growth.³¹¹ Biologics

305. See Sorscher, *supra* note 17, at 302.

306. *Biobetters Versus Biosimilars*, *supra* note 4 (eluding to biobetters potentially being a "once-a-day" dosing regime, which could treat the same indications "but in a better and smarter way").

307. Regulatory exclusivity for manufacturing methods may provide the industry with the extra inertia to innovate. See Price, *Innovation Policy Failures*, *supra* note 8, at 349 (arguing that, currently, regulatory exclusivity has only played a role in drug development and not for manufacturing methods); see also Price & Rai, *supra* note 42, at 189 (incentivizing disclosure with accelerated review and mandating disclosure attempts to increase competition and innovation).

308. Tucker & Wells, *supra* note 39, at 104 (recognizing "that brand reformulation strategies (often called 'product hopping' or 'evergreening')" may result in "change[s] in safety, purity, or potency"); see also Levy, *supra* note 235, at 276–79 (laying out how generic firms may succeed on antitrust claims based on a product hopping).

309. Tucker & Wells, *supra* note 39, at 101–02.

310. See Price, *Innovation Policy Failures*, *supra* note 8, at 346 (asserting that "quality through testing creates major inefficiencies and slows the production" while quality by design builds quality into the manufacturing process).

311. Potentially creating an independent pathway to validate new technologies outside of the NDA and BLA process would provide ROI viability options. *Id.* at 353.

manufacturing processes and the analytical tools that quantitatively compare biological products are the backbone of innovation in the biological products market. Because precision medications and rare disease treatments require high initial investments, which are not properly incentivized within the BPCIA, the biologics landscape is poised for change. The FDA will play a crucial role, both by regulating adaptively and by incentivizing disclosure proportional to high-quality innovation.³¹² As science and technology advances, applicants will possess more data to characterize the biopharmaceutical they are disclosing; however, competitors will simultaneously need less information to innovate upon prior art. Therefore, data exclusivity grants are particularly important over the next couple decades for ensuring consumers have the opportunity to use cheaper, biobetter medicines in the rare disease medication market.

CONCLUSION

Generally, the pharmaceutical market can be divided into two types of drugs: (1) small-molecule chemical compounds and (2) large complex molecule biologics. Descriptively, biologic chemotherapies, such as Herceptin and Rituxan, are referred to as “smart bombs,” no doubt because of their advantageous structural and functional make-up. However, because of biologics’ complex, large molecule nature, it is impossible to make an exact copy of a biologic; unlike small-molecule chemical compounds where generic replicates can be made, the best an FOB can hope for is a “biosimilar” label. R&D costs are high because of biologics complex structure and manufacturing difficulties. Thus, the BPCIA must incentivize biological product enhancements—whether developed by the reference product or the FOB sponsor—that result from improved manufacturing processes, producing consistent, lower priced options for consumers.

The proposed incentive structure within 42 U.S.C. § 262(k)(7)(B) incentivizes a sponsor to pursue a ROI in accordance with specific attributes of its manufacturing process. Within the current scheme, it is feasible for a biosimilar to be similar enough to qualify as a biosimilar under the BPCIA but not similar enough to be covered by a patent claim. Thus, pioneer manufacturers should take care in obtaining valid, optimal claims that afford broad patent protection of their biologics.

For examples of how biosimilars and biobetters are likely to dynamically and strategically capture market share, see *Biobetters Versus Biosimilars*, *supra* note 4.

312. *Manufacturing Barriers*, *supra* note 253, at 1063.

Until now, the pharmaceutical industry has focused on patents that protect the drug itself rather than methods of its manufacture. However, if manufacturers could renew their data exclusivity period in return for manufacturing improvements and additional scientific disclosure, consumers will reap the benefits. Additionally, by creating a one- to four-year data exclusivity extension opportunity, manufacturers will feel more comfortable reinvesting their ROI in manufacturing efficiency and manufacturers can capitalize on the complex-molecule nature of their biologic by exploring manufacturing drift.

Biologics developed through biotechnology constitute an essential part of the pipeline for medicines available to patients today and continue to grow at an increasing rate. The legislature should reinforce innovation and adaptation in this evolving area of science by providing incentives for a more robust biologic disclosure system.

The manufacturing processes used to develop biologics are highly valuable; some processes are protected as trade secrets while others are subject to patent protection. Biologics are developing in response to the inefficiencies of small-molecule pharmaceuticals, so it is increasingly important that the biologics market does not suffer from the same stagnation. By shifting manufacturers' focus from the risks of competition to the advantages of data exclusivity, more consumers will prescribe to the value of biologics for their own ailments and the same inefficiencies that plagued the small-molecule pharmaceutical market will be eliminated.