The Biosimilar Action Plan: An Effective Mechanism for Balancing Biologic Innovation and Competition in the United States?

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The strain between balancing pharmaceutical innovation and competition in the United States ("U.S.") centers around the need to ensure that the U.S. continues to encourage medical innovation while simultaneously providing patients with access to affordable and innovative drug treatments. This tension exists whether the drugs at issue are chemically-synthesized or complex large molecule drugs, such as biologics. In 2010, Congress passed the Biologic Price Competition and Innovation Act ("BPCIA"). The statute created a statutory approval pathway for biological products shown to be biologically similar ("biosimilar") to the originator or "brand" biologic while retaining the same safety, purity, and potency as the brand. Unfortunately, the BPCIA's provisions failed to accelerate biosimilar product development in the U.S., and the U.S. continues to trail behind Europe in providing patient access to affordable biosimilars.[1]

To help stimulate the U.S. biosimilar market, the Food and Drug Administration ("FDA") issued the Biosimilar Action Plan ("BAP") in July 2018. BAP focuses on four key strategies: (1) streamlining the biosimilar approval and product development process; (2) increasing biosimilar informational resources; (3) maximizing scientific and regulatory clarity; and (4) "getting competitively priced biosimilars into the market by reducing gaming of FDA requirements or other attempts to unfairly delay competition."[2]

An enhanced informational platform and a streamlined approval process should accelerate biosimilar product development and increase biosimilar approval rates. However, the FDA's regulatory powers are insufficient to curb the gaming and other anticompetitive behaviors that most negatively impact access, such as: (1) rebating schemes; (2) pay-for-delay agreements; (3) leveraging innovator patent rights to impede biosimilar market entry; and (4) other regulatory abuses.[3] Partnerships with key stakeholders, such as Congress, the Federal Trade Commission, States, Non-Governmental Organizations, and Payors are therefore crucial to achieving the BAP's overarching goal of "promoting competition and affordability [of biosimilars] across the market."[4] The recently proposed Biologic

1. *See* U.S. FOOD & DRUG ADMIN., BIOSIMILARS ACTION PLAN: BALANCING INNOVATION AND COMPETITION 1, 1 (2018), https://www.fda.gov/media/114574/download (on file with *The University of the Pacific Law Review*) (noting the FDA's responsibility for insuring that the balance between innovation and competition is equally important for traditional molecules, complex products, and biologics given their "critical roles in advancing the health of patients.").

2. *Id.* at 5–7.

3. *See, e.g.*, Tucker Herbert, Vartika Pandya & Ross Shahinian, *Can the FDA's Biosimilar Action Plan Change the Game for Biosimilars in the U.S.*, THE ACTIVE INGREDIENT (Oct. 17, 2018), https://info.zs.com/activeingredient/can-the-fdas-biosimilars-action-plan-change-the-game-for-biosimilars-in-the-u.s (on file with *The University of the Pacific Law Review*).

4. Scott Gottlieb, *Dynamic Regulation: Key to Maintaining Balance Between Biosimilars Innovation and*

Patent Transparency Act provides an example of how Congress can work in tandem with the FDA and other stakeholders to foster innovation and build a competitive and sustainable biosimilar marketplace for patients in the United States.

I. INTRODUCTION

"Congress has given the [FDA] . . . responsibility for implementing laws intended to strike a balance between encouraging and rewarding innovation in drug development and facilitating robust and timely market competition [patient access]."[5]

The tension between balancing pharmaceutical innovation and competition in the U.S. is driven by the need to ensure that the U.S. continues to encourage medical innovation without sacrificing the ability to provide patients with access to innovative drug treatments. Striking this balance is equally important for chemically-synthesized drug treatments as it is for more complex drugs, such as biologics.

Biological products or "biologics" are large molecule drugs[6] that are manufactured in, composed of, or derived from living systems such as animals or microorganisms.[7] Biologics include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy tissues, and recombinant therapeutic proteins. Unlike small molecule, chemically-synthesized drugs, biologics are comprised of complex molecular structures that are highly unstable and sensitive to even small changes in the manufacturing process. Also, because of their ability to trigger unwanted immune responses in the body, biologics are subject to more strenuous quality measures during production and more rigorous immunogenicity assessments during the FDA approval process.[8] As a result, biologics cost hundreds of millions of dollars to produce, which makes

Competition, U.S. FOOD & DRUG ADMIN. (July 18, 2018), https://www.fda.gov/news-events/speeches-fda-officials/dynamic-regulation-key-maintaining-balance-between-biosimilars-innovation-and-competition-07182018 (on file with *The University of the Pacific Law Review*).

5. U.S. FOOD & DRUG ADMIN., *supra* note 1, at 1.

6. TEVA, *supra* note 6, at 4 (on file with *The University of the Pacific Law Review*) *(*as distinguished from chemically based or "small molecule" drugs which are less complex and easy to manufacture. Chemical or small molecule drugs: (1) are stable and chemically synthesized; (2) have a low molecular weight; (3) are easily reverse engineered due to their "well-defined structure and manufacturing process"; (4) are mostly process independent with completely characterized chemicals. In sharp contrast, biologics: (1) have high molecular weight: (2) are strongly process dependent; (3) "impossible to fully characterize their molecular composition and heterogeneity" and (4) unstable and "sensitive to external conditions.").

7. *See* 42 U.S.C. § 262 (i)(1) (2018), *amended by* Further Consolidated Appropriations Act, 2020, Pub. L. No. 116–94, § 605, 133 Stat. 2534, 3127 (2019) (defining a biologic or "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.").

8. *Id.*

their production exponentially more expensive than small molecule drugs.[9] These exorbitant costs are reflected in the retail price paid for biologics.[10] For example, the retail cost for biologics used to treat rheumatoid arthritis ("RA") range from $18–$23k per year, compared to the significantly lower annual cost of $1.5–$2k for small molecule, chemically-synthesized RA drugs.[11] At the extreme end of the pricing[12] spectrum, the newly approved gene therapy Zolgensma, will be used to treat spinal muscular atrophy at a cost of about $2.1M per treatment.[13]

Despite their high costs, biologics are the best option for treating some of the most confounding diseases, including cancer and autoimmune disorders such as multiple sclerosis and Crohn's disease. Unfortunately, due to the high cost of manufacturing biologics,[14] only 2% of the U.S. population has access to these vital

9. Yaniv Heled, *Cheaper Versions of the Most Expensive Drugs May be Coming, but Monopolies Will Likely Remain,* THE CONVERSATION (June 4 2019), http://theconversation.com/cheaper-versions-of-the-most-expensive-drugs-may-be-coming-but-monopolies-will-likely-remain-117573 (on file with *The University of the Pacific Law Review*).

10. *See* Rob Stein, *At $2.1 Million, New Gene Therapy is the Most Expensive Drug Ever,* NPR (May 24, 2019), https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever (on file with *The University of the Pacific Law Review*) (noting that the newly approved gene therapy drug Zolgensma (used to treat spinal muscular atrophy) cost $2.1 million per patient).

11. *See, e.g.,* Julie Appleby, *Arthritis Drugs Show How U.S. Drug Prices Defy Economics*, KAISER HEALTH NEWS (Dec. 22, 2017), https://khn.org/news/arthritis-drugs-show-how-u-s-drug-prices-defy-economics/; *see* Jennifer Freeman, *RA Treatment Costs: What are the Costs of RA Medications and Surgery*, RHEUMATOID ARTHRITIS SUPPORT NETWORK (Oct. 27, 2018), https://www.rheumatoidarthritis.org/treatment/costs/ (on file with *The University of the Pacific Law* Review). Unfortunately, RA drugs are not the most expensive biologics on the market. For example, monthly treatments for the cancer drug Gleevac are estimated at $9,000 per /month and in 2017 dozens of cancer drugs cost over $100,000 per year in the U.S. *See, e.g.*, Jessica Merrill, *Remember When Provenge's Price Was Bold? Every New Cancer Drug in 2017 Cost $100,00 or More*, PHARMA INTELLIGENCE, https://pharmaintelligence.informa.com/resources/product-content/every-new-cancer-drug-in-2017-cost-100000-or-more (last visited Feb. 5, 2020) (on file with *The University of the Pacific Law Review*); Joshua Cohen, *The Curious Case of Gleevec Pricing*, FORBES (Sept. 12, 2018), https://www.forbes.com/sites/joshuacohen/2018/09/12/the-curious-case-of-gleevec-pricing/#586b399854a3 (on file with *The University of the Pacific Law Review*);

see also W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation,* 101 IOWA L. REV. 1023, 1027 (2016) ("Although prescribed less frequently than small molecule drugs, the average daily cost of biologics is 22 times higher than small molecule drug therapies.") (citing Elizabeth Richardson, *Biosimilars: To Encourage Competition, the Health Care Law Directs the FDA to Develop an Accelerated Approval Pathway for Follow-on Versions of Original Biologic Products*, HEALTH AFF. (Oct. 10, 2013), https://www.healthaffairs.org/do/10.1377/hpb20131010.6409/full/healthpolicybrief_100.pdf (on file with *The University of the Pacific Law Review*).

12. STEIN, *supra* note 10.

13. *Id.* (Novartis set the price at $2.125 million but offers insurers the ability to pay $425,000 a year for five years. This price tag makes Zolgensma the most expensive drug ever approved.").

14. In comparison, the cost of producing small molecule drugs are relatively low due to the relatively straightforward manufacturing process and the ability to clinically test on animals without worrying about immunoresponses. Also, small molecule, chemically synthesized drugs are far less expensive to produce and market than biologics. Biologic development is uniquely difficult because unlike chemically synthesized drugs, animals cannot be used to simulate the potential immunogenic response that a human might have to a biologic. *See* Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1, 8 (2018); Price II & Rai, *supra* (noting the daily cost of a biologic is twenty-two times the cost of a chemically synthesized drug).

pharmaceuticals. Yet, these drugs account for 40% of prescription drug spending in the U.S.[15] From the outset of this disparity, Congress saw the need to create a framework for providing greater access to less expensive versions of brand biologics without deterring continued innovation in this space. They hoped to mirror the 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Amendments ("Hatch-Waxman")),[16] which provided an accelerated FDA approval pathway for generics and a framework for the premarket resolution of patent disputes.[17]

Congress designed Hatch-Waxman to increase patient access to generic small molecule drugs, without sacrificing the incentives necessary to foster continued pharmaceutical innovation.[18] To achieve this balance, the Act provides an abbreviated FDA approval pathway for generics[19], while giving manufacturers of the brand or "reference" drug a five-year period of clinical trial data exclusivity.[20] Overall, Hatch-Waxman met its goal of balancing access and innovation. Within ten years of enactment, innovative brands experienced a seven to twelve-year increase in patent enforceability, while the number of prescriptions filled with generics increased from 19% to 88%.[21]

In 2010, Congress passed the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which created a statutory approval pathway for biological products shown to be biosimilar to or interchangeable with originator biological products.[22] Like Hatch-Waxman, the BPCIA was enacted to strike a balance

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15. Aydin Harston, *FDA's Biosimilar Approvals Accelerate in 2018: How the U.S. Compares to Europe on Biosimilar Approvals and Products in the Pipeline*, ROTHWELL FIGG (Feb. 5, 2019), https://www.biosimilarsip.com/2019/02/05/fdas-biosimilar-approvals-accelerate-in-2018-how-the-u-s-compares-to-europe-on-biosimilar-approvals-and-products-in-the-pipeline/ (on file with *The University of the Pacific Law Review*); Andrew W. Mulcahy, Jakub P. Hlavka & Spencer R. Case, *Biosimilar Cost Savings in the United States* 1, 2, RAND HEALTH CORP.. (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075809/ (on file with *The University of the Pacific Law Review*); U.S. FOOD & DRUG ADMIN., *supra* note 1, at 1.

16. Hatch-Waxman Act of 1984, 21 U.S.C. § 355 (2018).

17. *See* Erika Leitzan, *The Unchartered Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. U. L. REV. 883, 885–86 (2017).

18. *See* LEITZAN, *supra* note 17, at 932.

19. The Act allows generics to file an Abbreviated New Drug Application (ANDA) in which it must establish that the "generic possesses the same active ingredient, route of administration, bioequivalence (rate and extent of drug absorption) and other characteristics as the brand version." CARRIER & MINNITI, *supra* note 14, at 12.

20. *See* 21 U.S.C. § 355 (j)(5)(F)(ii) (making clear that during this time, generic drug manufacturers are prohibited from filing abbreviated applications for a posed duplicate of variation of the "reference product.").

21. *See* ASS'N ACCESSIBLE MED., 2018 GENERIC DRUG ACCESS & SAVINGS IN THE U.S. 1, 4 (2018) (on file with *The University of the Pacific Law Review*) (according to the AAM 2018 Generic Drug Access and Savings Report, the Hatch-Waxman Act led to $265 billion of savings in 2017, and approximately $1 trillion in savings over the past decade).

22. *See* 42 U.S.C. § 262(k) (2018); *Biosimilar Product Information*, U.S FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm (last updated July 3, 2019) (on file with *The University of the Pacific Law Review*); U.S. FOOD & DRUG ADMIN., *supra* note 1, at 1; Ameet Sarpatwari et al., *The US Biosimilar Market: Stunted Growth and Possible Reforms*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 92, 93 (2019); Christine Coughlin et al., *Regenerative Medicine and the Right to Try*, 18 WAKE

between patient access and pharmaceutical innovation. The Act provides a period of exclusivity for originator biologics, enabling an abbreviated approval pathway for competitive biosimilars once the twelve-year data exclusivity period for the reference (originator) biologic lapses.[23] The abbreviated pathway allows a manufacturer to rely in part on the data evaluated during the FDA's previous determination for the referenced biologic to establish that the biosimilar product "is highly similar to the reference product notwithstanding minor differences in clinically inactive components."[24] Also, there can be no clinical differences between the biological product [biosimilar] and the reference product in terms of safety, purity, and potency.[25] The abbreviated pathway accelerates the FDA approval process.

In addition to accelerating the FDA approval process, the abbreviated pathway also lowers the overall production costs as allowing the biosimilar manufacturer to leverage the FDA's finding of safety and effectiveness for the reference biologic reduces the need for multiple large clinical outcomes studies as part of biosimilar product development.[26] Thus, the BPCIA offered the ideal platform for both increasing biosimilar production and providing greater access to affordable biologics, without sacrificing continued biologic innovation.[27]

Sadly, the BPCIA failed to accelerate biosimilar product development or increase biosimilar accessibility, and the U.S. continues to trail Europe in the approval and marketing of biosimilar products.[28] Subsequently, to jumpstart

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FOREST J. BUS. & INTELL. PROP. L. 590, 632 n.305 (2018).

23. Zachary Brennan, *New Study Question the Need for 12 Years of Market Exclusivity for Biologics*, REGULATORY FOCUS (June 21, 2019), https://www.raps.org/news-and-articles/news-articles/2019/6/new-study-questions-the-need-for-12-years-of-marke (on file with *The University of the Pacific Law Review*) (noting that professionals continue to debate the necessity of a twelve-year exclusivity period granted to manufactures of biologics when chemically synthesized drugs are limited to a five-year period of data exclusivity under the Hatch-Waxman Act, while the European Union provides ten years of exclusivity for both small-molecule drugs and biologics).

24. CARRIER & MINNITI, *supra* note 14, at 8.

25. SARPATWARI ET AL., *supra* note 22, at 93.

26. U.S. FOOD & DRUG ADMIN., *supra* note 1, at 2.

27. *Id.* (suggesting that this remains the FDA's hope and Congress's vision when enacting the plan); *see Examining Implementation of the Biologics Price Competition and Innovation Act: Hearing Before the Subcomm. on Energy and Commerce H.R.,* 114th Cong. 114–114 (2016).

28. Biosimilars have been available in Europe since 2006, with fifty-four currently available at discounts due to 80%. In 2018, "the U.S. spent $126 billion on biologic drugs, only 2% of it on biosimilars." Keith Srakocic, *Future is in Doubt for Cheaper Versions of Biologic Drugs*, NBC NEWS (June 27, 2019), https://www.nbcnews.com/health/health-news/future-doubt-cheaper-versions-biologic-drugs-n1023211(on file with *The University of the Pacific Law Review*) (https://www.nbcnews.com/health/health-news/future-doubt-cheaper-versions-biologic-drugs-n1023211 (reporting Europe's shorter monopoly-protecting patents and government control explains Europe's lead over the U.S. in the biologics space and describing U.S. in the "infancy" stage of biosimilar production); *see Advancing Biosimilar Sustainability in Europe,* IQVIA (Sept. 4, 2018), https://www.iqvia.com/en/institute/reports/advancing-biosimilar-sustainability-in-europe (on file with *The University of the Pacific Law Review*); 42 U.S.C. § 262 (i)(1) (2018), *amended by* Further Consolidated Appropriations Act, 2020, Pub. L. No. 116–94, § 605, 133 Stat. 2534, 3127 (2019) (noting the FDA's inability to potentially limit monopolies even with the push for production of small-molecule drugs).

Congress's intended outcome, the U.S. FDA issued the Biosimilar Action Plan ("BAP"). The BAP is Congress' most recent attempt to supplement the BPCIA by creating a regulatory framework that stimulates biosimilar product development, while preserving the incentive to produce next-generation biologics.[29]

Increasing biosimilar informational resources and streamlining the FDA application and approval process are two of BAP's four key strategies.[30] As the regulatory agency that controls the drug approval process, the FDA possesses the direct authority to streamline the approval process, provide greater regulation clarity, and enhance informational resources to incentivize biosimilar product development.[31] The BAP is achieving these two goals as evidenced by at least sixty ongoing biosimilar development programs and the increased rate of biosimilar drug approval.[32] The FDA's regulatory power is insufficient, however, to implement the BAP strategy that holds the greatest potential for impact on increasing patient access to affordable biosimilars: "getting competitively priced biosimilars into the market by reducing the gaming of FDA requirements and other attempts to unfairly delay competition."[33] While the FDA has demonstrated strength in providing adaptive regulation-enhancing regulatory schemes to facilitate innovation and competition, anti-competitive behavior such as rebate schemes and pay-for-delay agreements are typically within the purview of Congress, the courts, and agencies such as the Federal Trade Commission ("FTC") and the Department of Justice ("DOJ").[34]

This article proposes that while it is a step in the right direction, the Biosimilar Action Plan is insufficient to break the stronghold that originator biologic manufacturers currently have on the biologic market in the United States. As noted by NBC Health News, the current pricing and competitive landscape put "the future in doubt for cheaper versions of biologic drugs."[35]

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29. U.S. FOOD & DRUG ADMIN., *supra* note 1, at 1.

30. *Id.* at 5 (listing BAP's other priority deliverables as: (2) "maximizing scientific and regulatory clarity"; (3) developing effective communications aimed at improving understanding of biosimilars; and (4) supporting market competition, notably by "reducing gaming of FDA requirements or other attempts to unfairly delay competition.").

31. *See, e.g.,* HERBERT, PANDYA & SHAHINIAN, *supra* note 3 (for example, under Hatch-Waxman, the FDA expedited the approval process for generic drugs by allowing generics to rely on data supplied by the brand drug during its approval process.); U.S. FOOD & DRUG ADMIN., *supra* note 1, at 2.

32. U.S. FOOD & DRUG ADMIN., *supra* note 1, at 2.

33. *See* HERBERT, PANDYA & SHAHINIAN, *supra* note 3; *see also FDA Biosimilars Plan Draws From Experience with Generics,* LAW 360 (Aug. 20, 2018), https://www.law360.com/articles/1074759/fda-biosimilars-plan-draws-from-experience-with-generics (on file with *The University of the Pacific Law Review*) (although former FDA Commissioner Gottlieb acknowledged that BAP provides strategies and proposed deliverables "'aimed at promoting competition and affordability across the market' it does not address issues" that fall outside the FDA's jurisdiction, such as "(1) 'rebating schemes' and (2) 'patent thickets' resulting in litigation delayed market entry."); Gottlieb, *supra* note 4; *cf*. Coughlin et al., *supra* note 22, at 616–22.

34. *See, e.g.*, CARRIER & MINNITI, *supra* note 14, at 36.

35. SRAKOCIC, *supra* note 28; *see also* Hillel P. Cohen & Dorothy McCabe, *Combatting Misinformation on Biosimilars and Preparing the Market for them Can Save the U.S. Billions*, STAT (June 19, 2019), https://www.statnews.com/2019/06/19/misinformation-biosimilars-market-preparation/ (on file with *The University of the Pacific Law Review*).

This article begins by describing the science behind biologics and the complexity of the biologic manufacturing process. Part II outlines the key provisions of the 2010 Biologic Price Competition and Innovation Act ("BPCIA"), which created the accelerated approval pathway and pre-approval patent infringement litigation framework (the "patent dance") for biosimilars. The BPCIA's twelve-year data exclusivity and patent dance provisions incentivized continued biologic innovation. The Act has failed, however, to increase biosimilar production and create a thriving and competitive biosimilar market in the United States.

Part III outlines the BAP's four key regulatory strategies and their related product deliverables, which are "aimed at promoting competition and affordability [of biosimilars] in the United States."[36] This section evaluates the positive impact the FDA could have through specific "priority deliverables," such as enhancing informational resources and further streamlining the FDA approval process for biosimilars. It then argues that the FDA, as a regulatory agency, lacks the bandwidth to provide the most crucial deliverable-reducing anticompetitive behavior and getting competitively-priced biosimilars into the market.

Part IV of this article posits that the FDA must partner with key stakeholders such as Congress, the Federal Trade Commission ("FTC"), Payors, and Non-Governmental Organizations ("NGO's") to curb the misinformation, litigation, gaming and other pricing tactics that originator biologic manufacturers use to impede biosimilar market entry. These partnerships can create statutory, regulatory, pricing and data access platforms that will invigorate the fledging biosimilar market in the U.S., while simultaneously preserving the incentive to produce next-generation biologics. The article concludes by offering the recently proposed Biologic Patent Transparency Act as an example of how Congress can work in tandem with the FDA and other stakeholders to foster competition and build a competitive and sustainable biosimilar marketplace for patients in the U.S.

II. BIOLOGICS 101

Biologics are complex drugs of heterogeneous structure produced from living cells. For this reason, the manufacturing process for a biologic is imperative and must be followed exactly.[37]

Biological products ("biologics") are highly unstable chemical structures that are heat sensitive and susceptible to microbial contamination.[38] Yet, they represent

36. GOTTLIEB, *supra* note 4.

37. TEVA, *supra* note 6, at 4.

38. FDA, *What are "Biologics" Questions and Answers,* U.S. FOOD & DRUG ADMIN. (Feb. 06, 2018), https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers (on file with *The University of the Pacific Law Review*).

the cutting-edge of biomedical research.[39] Biologics are large molecule drugs that are isolated from a variety of natural resources and are manufactured in, composed of, or derived from living systems such as animals or microorganisms.[40] In sharp contrast, traditional small molecule drugs are fairly stable and derived through chemical synthesis, making it relatively simple and much less expensive to create generic versions of innovator drugs.[41] Biologics can be composed of sugar, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.[42] We will briefly describe the process for creating therapeutic proteins, the most commonly manufactured biologic in the Unites States.[43]

The manufacturing process for a therapeutic protein begins with the selection of the cell line ("host cell") that will eventually produce the biologic.[44] The starter population is typically selected from bacteria, yeast, mice, hamster or monkey cells.[45] Next, a random amount of the DNA encoding the protein of interest is added to the cells;[46] the cells are then isolated, grown into populations and evaluated for growth and production rates.[47] After the culture medium is optimized, the cells are grown in the complex and variable production environment of large-scale bioreactors.[48] Once production is complete, it takes several steps to isolate and purify the protein.[49] According to Teva pharmaceuticals, all

39. *Id.*

40. *Id.*

41. CARRIER & MINNITI, *supra* note 14, at 7 (discussing the predictability of chemical synthesis of traditional drugs, thereby allowing generics to imitate brands at low cost v. biologics, which "blow up that paradigm" since the product is actually the process, which creates "higher variability and follow-ons cannot precisely replicate the original product."); *see also* Price & Rai, *supra* note 11, at 1026 (describing the ease of creating chemically synthesized generic drugs and contrasting the weight of large molecule drugs with small molecule drugs, like aspirin. Stating "if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet.").

42. FDA, *supra* note 38.

43. PRICE & RAI, *supra* note 11, at 1027; *see also* CARRIER & MINNITI, *supra* note 14, at 7–8 (describing how the four-different hierarchal/structural levels of therapeutic proteins (primary, secondary, tertiary and quaternary) can be modified in various ways through their synthesis by the living source. The primary structure contains the amino acid sequence which is key for essential biologic activity, making them extremely path dependent and uniquely unstable.); *Important Safety Information About Humira,* HUMIRA ADALIMUMAB, https://www.humira.com (last visited Aug. 28, 2019) (on file with *The University of the Pacific Law Review*) (listing the different illnesses https://www.humira.com (Humira, an example of a mouse-human chimeric antibody that is used to treat rheumatoid arthritis, psoriatic arthritis and Crohn's disease).

44. TEVA, *supra* note 6, at 12; Price & Rai, *supra* note 11, at 1023–24; CARRIER & MINNITI, *supra* note 14, at 5.

45. The choice of organism from which to generate a cell line, and the culture conditions can affect glycosylation—or the "binding of carbohydrate molecules" to the protein which can affect half-life or a patient's immune response. *See* PRICE II & RAI, *supra* note 11, at 1034–35; *see also* TEVA, *supra* note 6, at 14.

46. More specifically, the DNA for the biological product is "attached to a vector (such as a virus), and transferred to a host cell, which will make the biologic product." TEVA, *supra* note 6, at 12.

47. TEVA, *supra* note 6, at 12; *see also* PRICE & RAI, *supra* note 11, at 1035 (additionally, DNADVA selection can help "increase the number of copies, stability, and growth rate of the eventual final cell line.").

48. Price & Rai, *supra* note 11, at 1035.

49. *Id*.

manufacturing processes have inherent variability, and some degree of variability is normal during the manufacturing process.[50] Thus, throughout this process, it is necessary for biologic manufacturers to monitor and ensure that the variability of various "Critical Quality Attributes (CQA's) or characteristics" of the biologics is normal in comparison to the variability of the drug product.[51]

Biologics can be defined according to their source material and manufacture.[52] However, the complex mixtures of chemical that form biologics, cannot be easily identified or characterized.[53] The process of characterizing and manufacturing biologics is complicated by the nature of biologics and the variability between each manufacturing process. These same challenges are often absent in the sphere of small molecule drug manufacturing.[54] Since the active substances in biologics are often too complex to be fully characterized by utilizing physiochemical testing methods alone and differ from one preparation method or batch to the next[55], it is necessary to use strict aseptic principles during manufacturing.[56]

Manufacturers are required to ensure activities associated with the handling of live biological agents are contained in such a way to prevent contamination of the live agents and outside environment.[57] This is regulated by the Good Manufacturing Practices ("GMP") for biologics, which were first published by the World Health Organization ("WHO") in 1992.[58] Since biologics are manufactured in or composed of cells or microbial organisms, production of biologics must be controlled to prevent unwanted bioburden, endotoxins, viruses of animal and human origin, and associated metabolites.[59] The inoculum preparation, growth media, and manufacturing equipment must be sterilized, often by heat or microbial-retentive filters.[60]

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50. TEVA, *supra* note 6, at 15 (explaining that over time, changes in "either the manufacturing process or quality attributes" of the biologic can lead to drift which is the "unintended, unexplained, or unexpected change in either [the] manufacturing process parameters or the final product" of the product's lifetime).

51. *Id.* at 13–15 (these issues include: (1) protein structure: an incorrect structure can lead to reduced or variable drug efficacy; (2) The binding of carbohydrate molecules to the protein (glycolsylation)-variations can effect a patient's immune response to the biologic or affect the drug's half-life; (3) biological activity: "the ability to bind to its molecular target"; and (4) manufacturing process impurities).

52. *WHO Good Manufacturing Practice for Biological Products,* WORLD HEALTH ORG. (2016), *available at* https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf (on file with *The University of the Pacific Law Review*).

53. FDA, *supra* note 38.

54. *Biological Product Definitions,* U.S. FOOD & DRUG ADMIN. https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf (last visited Aug. 29, 2019) (on file with *The University of the Pacific Law Review*).

55. *WHO Good Manufacturing Practice for Biological Products, supra* note 52.

56. FDA, *supra* note 38.

57. *WHO Good Manufacturing Practice for Biological Products, supra* note 52.

58. *Id.*

59. *Id.*

60. *Id.*

Additionally, the WHO and the FDA heavily regulate the production of biologics, enforcing regulations that require extreme sterilization and air-handling systems in all biologic manufacturing facilities.[61] Further, the FDA assesses the manufacturing process and the manufacturer's strategy to control same-batch product variations.[62] These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.[63]

While biologics are effective, they are expensive and highly unstable products. The process for creating the highly unstable drug grows in complexity as the need to protect consumers from contamination increases. The strict manufacturing regulations to produce the large molecule drug ensures consistent clinical performance but presents challenges that continuously increase the overall cost of biologics, for both the consumer and manufacturer.

III. THE BIOLOGIC PRICE COMPETITION AND INNOVATION ACT (BPCIA) FAILED TO MEET ITS GOAL OF STRIKING THE APPROPRIATE BALANCE BETWEEN INCENTIVIZING BIOLOGIC INNOVATION AND FACILITATING INCREASED BIOSIMILAR ACCESS

In 1984, Congress enacted a statute permitting approval for generic copies of innovative drugs. Twenty-six years later, it enacted a statute permitting licensure of biosimilar versions of innovative biological medicines, and simply put, we're not in Kansas [Dorothy's home in the Wizard of Oz] anymore.[64]

In 1984, Congress passed the Hatch-Waxman Act ("Hatch-Waxman") to accelerate the production of lower-cost generic versions of small molecule (traditional) brand drugs, while serving continued innovation in this space.[65] A generic drug is the therapeutic equivalent of an innovator brand drug and must be identical in active ingredient, dosage, administration and safety. For decades, the time-consuming and expensive process to obtain FDA approval for generics prevented these companies from effectively competing with brand manufacturers to offer affordable generic versions of innovator drugs.[66] Hatch-Waxman altered this landscape by providing an abbreviated pathway for the approval of small molecule generics where the drug applicant is allowed to file an Abbreviated New Drug Application ("ANDA").

Under Hatch-Waxman, a company must show that its generic drug possesses

61. *Biological Product Definitions, supra* note 54.

62. *Id.*

63. *Id.*

64. Leitzan, *supra* note 17, at 884.

65. Hatch-Waxman Act of 1984, 21 U.S.C. § 355 (2018) (noting that in passing Hatch-Waxman, "the legislature sought to increase generic competition and foster innovation.").

66. Leitzan, *supra* note 17, at 893–902; *see* Carrier & Minniti, *supra* note 14, at 8 (explaining the pre-Hatch-Waxman landscape and noting that it took Hatch Waxman's abbreviated approval process to enable generics to offer a lower-cost and more accessible option to innovator brand drugs).

the same active ingredient, route of administration, bioequivalence (rate and extent of drug absorption), and other characteristics as the brand or "originator" drug.[67] The ANDA allows a generic to bypass its own clinical trials and rely on the originator's clinical data to demonstrate that it meets the FDA's safety and effectiveness standards.[68] Originators must also identify patents they believed will be infringed by the generic and disclose them in a FDA publication known as the "Orange Book."[69] Hatch-Waxman also addressed the "launching-at-risk" problem faced by generics who risked being sued for patent infringement during the FDA approval process and before launching their product on the market. The Act's special litigation scheme arms federal courts with subject-matter jurisdiction in a patent infringement suit based solely on the generic drug company's application for FDA approval to market its drug.[70] Paragraph IV of the Act provides a certification process that allows the generic (ANDA applicant) to utilize the information disclosed in the orange book to challenge the validity of an originator's disclosed patent so that it may enter and utilize the patented material during the patent term.[71]

In exchange for allowing the generic to leverage its clinical data to obtain FDA approval, the originator receives a five (5) year period of clinical data or regulatory exclusivity.[72] During this exclusivity period, competitors are prevented from using the originator's data to produce generic versions of the reference drug.[73] Also, Congress granted to patent holders, that sue within forty-five days of receiving a

67. Hatch-Waxman Act of 1984, 21 U.S.C. § 355 (2018); Jeffrey A. Hovden, *Pharmaceutical Patent Litigation Strategies,* LEXISNEXIS (June 22, 2018), https://www.lexisnexis.com/lexis-practice-advisor/the-journal/b/lpa/posts/pharmaceutical-patent-litigation-strategieshttps://www.lexisnexis.com/lexis-practice-advisor/the-journal/b/lpa/posts/pharmaceutical-patent-litigation-strategies. During Hatch-Waxman litigation "a brand name drug company may be referred to as the innovator, the pioneer, the patent owner, the NDA (New Drug Applicant), or the RLD (reference-listed-drug) holder." Conversely, generic may be referred to as ANDA (abbreviated new drug application) Applicant or the ANDA Filer.

68. *See* 35 U.S.C. § 271(e) (2012) (the Patent Act also provides the experimental use exception that allows generic companies to experiment on patented drugs during the patent term).

69. CARRIER & MINNITI, *supra* note 14, at 12 ("The ANDA applicant (generic) must provide one of four certifications for each patent listed in the Orange Book.").

70. *See* 35 U.S.C. § 271(e)(5).

71. *Id.*; *see also* CARRIER & MINNITI, *supra* note 14, at 12 ("An incentive to encourage such filings, the Act allows the first Paragraph IV filer to obtain 180 days of exclusivity, which—because it allows the first Paragraph IV filer to obtain 180 days of exclusivity, which—because it allows generics to charge prices only modestly less than bran prices—is (as the Supreme Court recognized) a 'valuable' period worth several hundred million dollars.").

72. *See e.g.,* Michael Furrow & Whitney Meier, *Biosimilars and the Biologics Price Competition and Innovation Act (BPCIA),* LEXISNEXIS (Feb. 21, 2019), https://www.lexisnexis.com/lexis-practice-advisor/the-journal/b/lpa/posts/biosimilars-and-the-biologics-price-competition-and-innovation-act-bpcia (on file with *The University of the Pacific Law Review*). Commentators sometimes use the term "market exclusivity" rather than "data exclusivity" to describe this period when the originator has total market control of its product.

73. PRICE & RAI, *supra* note 11, at 1027 ("After that short exclusivity period, Hatch-Waxman treats the originator clinical trial data as information infrastructure whose social value is maximized through some level of competitor access.").

Paragraph IV notice, an automatic thirty-month stay of FDA approval.[74]

Combined, an originator's twenty-year patent property rights and Hatch-Waxman's five-year data exclusivity periods provide a level of pricing power that yields extraordinary profits for brand drug manufacturers and incentivizes continued innovation in the traditional drug space.[75] Thus, Hatch-Waxman's statutory framework achieved its goal of increasing patient access to generics and incentivizing innovation of small molecule drugs. Remarkably, within ten years of enactment, innovative brands experienced a seven to twelve-year increase in patent enforceability, while the number of prescriptions filled with generics increased from 19%–88%.[76]

Unfortunately, the complexity and process-driven nature of biologics prevents them from fitting neatly into a "Hatch-Waxman like" generic approval pathway.[77] Small molecule drugs are developed through predictable chemical synthesis processes. The final chemical compound is always the same and easily verified, which facilitates the duplication and manufacture of a generic "bioequivalent" for the reference drug.

Conversely, the biologics' complex and unstable molecular structure results in variation in batches of active ingredients in the biologic manufacturing process. This makes it virtually impossible to establish bioequivalence or "structural identity" to the originator or "reference"[78] biologic without access to intricate manufacturing process data that is generally a protected trade secret that is not disclosed during the reference biologic's FDA approval process.[79] Without access to this crucial information, it is impossible to duplicate the originator biologics quality measures and produce a generic biologic that is completely "interchangeable" with the reference drug.[80] As a result, Congress started from

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74. CARRIER & MINNITI, *supra* note 14, at 12 (citing FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY, at 5 (2002), https://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy_0.pdf (on file with *The University of the Pacific Law Review*)). Congress also allowed generics to avoid the expensive and lengthy new drug process by filing an Abbreviated New Drug Application ("ANDA"). To do this, a generic must show that its drug possesses the same active ingredient, route of administration, bioequivalence (rate and extent of drug absorption), and other characteristics as the brand version).

75. *Id*.

76. *Id.* at 13 (according to the AAM 2018 Generic Drug Access and Savings Report, the Hatch-Waxman Act led to $265 billions of savings in 2017, and approximately $1 trillion in savings over the past decade).

77. SRAKOCIC, *supra* note 28. Since the stability of chemical compounds, a generic version of a drug can easily be produced directly from the reference product data disclosed during the FDA approval process at a cost of about $2 million and a two-year timeframe. Manufacturing costs of chemically synthesized drugs are estimated at pennies per pill. Thus, generic manufacturers can remain profitable and offer price points up to 90% lower than the brand competition.

78. The FDA refers to the originator biologic as the reference drug because its data is what is what the biosimilar relies on or "references" to bypass certain clinical trial data and gain accelerated FDA approval.

79. PRICE & RAI, *supra* note 11, at 1028 (noting that "much less is discussed and more profound in the long term, is the significant barrier to biologic market entry that may persist indefinitely as a consequence of the trade secrecy pervasive in the field of biologic manufacturing.").

80. Of course, promoting interchangeable biologics is the ideal platform since prescribers could easily choose the generic without fear of unknown immune responses or side effects, and pharmacies could substitute

ground zero to develop a framework for encouraging the development and approval of drugs that were less than exact copies of originator biologics, but had no clinically meaningful differences in terms of safety, purity, and potency.[81]

In 2010, Congress passed the Biologic Price Competition and Innovation Act of 2009 ("BPCIA"), as part of the Affordable Care Act, which created a statutory approval pathway for biological products shown to be biologically similar (biosimilar) to the originator or "brand" biologic, while retaining the same safety, purity, and potency as the brand, or interchangeable[82] with originator biological products.[83] Like Hatch-Waxman, the BPCIA was enacted to strike a balance between patient access and pharmaceutical innovation.[84] The Act provides a period of exclusivity for originator biologics and the Reference Product Sponsor ("RPS"). The Act also enables an abbreviated approval pathway for competitive biosimilars once the twelve year marketing exclusivity period for the reference (originator) biologic lapses.[85] The abbreviated pathway allows a manufacturer to rely in part

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the generic biologic for the interchangeable generic without physician approval. Some states have already relaxed laws relating to these requirements. What's potentially troubling is that NGO's are already promoting biosimilars as the ideal platform to provide access to the most vulnerable members of our populations, the poor and the elderly. David R. Gaugh, *Comments from The Association for Accessible Medicines (AAM) and the Biosimilars Council on Behalf of our Member Companies, Regarding Docket FDA-2018-N-2689, Facilitating Competition and Innovation in the Biological Products Marketplace, Public Hearing; Request for Comments*, BIOSIMILARS COUNCIL (Sept. 21, 2018), https://www.bigmoleculewatch.com/wp-content/uploads/sites/2/2018/10/AAM-Biosimilars-Council-Comments-on-FDA-2018-N-2689-FINAL-1.pdf (on file with *The University of the Pacific Law Review*). At least one scholar, has recently challenged this framework and argues that Congress and the FDA should change their focus from access to biosimilars and force biologics to become more transparent about their manufacturing processes to allow for the production of interchangeable, rather than biosimilar generics.

81. *See* 42 U.S.C. § 262(i)(2) (A biosimilar is "highly similar to the reference product notwithstanding minor differences in clinically active components", and has no "clinically meaningful differences from the reference product in terms of safety, purity and potency."); *see also Biological Product Definitions, supra* note 54 (explaining that clinically meaningful differences are generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, as assessment of clinical immunogenicity, and, if needed, additional clinical studies"); *see also* Leitzan, *supra* note 17, at 893 (discussing how unlike Hatch-Waxman, Congress started from scratch with the BCIA since biologics markets were newly developing).

82. *See* 42 U.S.C. § 262(k)(4) (an interchangeable product is a biosimilar for which the sponsor (applicant) has demonstrated that the biosimilar can be "expected to produce the same clinical result as the reference product in any given patient." Also, the sponsor must demonstrate that "the risk in terms of safety and diminished efficacy of switching between use of the interchangeable product and a reference product will not be greater than the risk of using the reference product without such switching."); *see also* Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, NATIONAL CONFERENCE OF STATE LEGISLATURES (Oct. 22, 2018), http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx (on file with *The University of the Pacific Law Review*) (although, the BPCIA provides for substituting biologics with interchangeable products, each state sets its own parameters concerning how, and when, biosimilars and interchangeable products can be substituted for the branded biologic and whether prescriber consent is required).

83. 42 U.S.C. § 262.

84. *See Examining Implementation of the Biologics Price Competition and Innovation Act: Hearing Before the Subcomm. on Energy and Commerce H.R.,* 114th Cong. 114–114 (2016) (as noted previously, this remains the FDA's hope and Congress's vision when enacting the plan).

85. *See generally* BRENNAN, *supra* note 23 (there was great debate over having a 12-year exclusivity for biologics since chemically synthesized drugs are limited to a 5-year period of data exclusivity under the Hatch-

on the data evaluated during the FDA's previous determination for the referenced biologic to establish that the biosimilar product "is highly similar to the reference product notwithstanding minor differences in clinically inactive components."[86] Also, there can be no clinical differences between the biological product [biosimilar] and the reference product in terms of safety, purity, and potency.[87] Biosimilarity is evaluated using analytical studies; like animal studies, including toxicity assessments of immunogenicity and pharmacokinetics or pharmacodynamics.[88]

To encourage continued biologic innovation, the BPCIA prevents biosimilar and interchangeable drug applicants from filing a 351(k)[89] abbreviated drug licensing application ("aBLA") for four years after the date the reference product's licensing date.[90] Also, while Hatch-Waxman provides five years of data or regulatory exclusivity for traditional originator drugs, under the BPCIA, the originator biologic or RPS benefits form an increased exclusivity period of twelve-years.[91]

In addition to the varying exclusivity periods, there are other notable differences between the framework for originator biologics subject to the BPCIA and the framework for small-molecule drugs subject to the Hatch-Waxman Act, including issues related to product complexity and pharmacy substitutions.

For example, under Hatch-Waxman, a generic must show that its drug possesses the same active ingredient, route of administration, bioequivalence (rate and extent of drug absorption), and other characteristics as the brand version. Under the BPCIA, aBLA sponsor must demonstrate that its product is "safe, pure, and potent," and that its manufacturing facility satisfies required standards; and a biosimilar must show that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive

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Waxman Act).

86. 42 U.S.C. §. 262(i)(2).

87. *Id.*

88. 42 U.S.C. § 262(k) (2010) (pharmacokinetics measures factors such as absorption and elimination of a drug, while pharmacodynamics measures the effects of the drug on its biological target); TEVA, *supra* note 6, at 32.

89. *See* TEVA, *supra* note 6, at 4 (the 351(k) application or "approval pathway) outlines the process for the FDA approval of a biosimilar drug, with the goal of demonstrating biosimilarity between the proposed biosimilar product and the reference product, not independently establishing the safety and effectiveness of the proposed product. In contrast, theoriginator biologic takes the Section 351(a) approval pathway, which must contain all data and information necessary to demonstrate its safety and effectiveness. This includes clinical trials for the disease indications being sought by the manufacturer).

90. 42 U.S.C. § §.262(k)(7)(B).

91. 42 U.S.C. § 261(k)(7)(A) (the biologic increased exclusivity period was hotly debated); *see e.g.*, Irena Royzman & Nathan Monroe-Yavneh, *Twelve Years, or Fewer? Two Current Debates on the Exclusivity Period for Biologics*, Patterson Belknap: Biologics Blog (Feb. 24, 2015), https://www.biologicsblog.com/twelve-years-or-fewer-two-current-debates-on-the-exclusivity-period-for-biologics (the BPCIA allows additional extensions of exclusivity (seven years) for orphan drugs specifically approved for treating a condition affecting 200,000 or less, or if the RPS goes through FDA requested pediatric studies (6 months)); *see* 21 U.S.C. § 360b (orphan drugs); *see also* 42 U.S.C. § 262(m).

components; and . . . there are no clinically meaningful differences between the biological product and the reference product in term of safety, purity, and potency of the product."[92]

Other notable differences include the lack of patent linkage for biosimilars and the lack of a patent list or "Orange Book" for biosimilars.[93] These differences may result in different market dynamics. Nonetheless, the new legal framework for biosimilars is similar to the framework created under the Hatch-Waxman amendments in that it provides a pathway under which increased competition has the potential to emerge.

Like Hatch-Waxman, the BPCIA establishes a framework for exchanging information and conducting patent litigation to clear patent rights prior to the marketing of the biosimilar product.[94] Known as the "patent dance," this process begins when a biosimilar applicant chooses to disclose its aBLA application to the RPS, along with detailed information concerning its biosimilar manufacturing process.[95] In *Sandoz v. Amgen*,[96] the Supreme Court confirmed that the biosimilar (aBLA) applicant is not required to submit its aBLA application to the RPS, and the RPS cannot force this disclosure.[97] If the applicant chooses to submit the aBLA application, however, the RPS has sixty days from receiving the aBLA to provide a list of patents for which it believes it could bring a patent infringement claim against non-licensed aBLA applicants, any patents that could be "potentially

92. 42 U.S.C. § 262(i)(2) ("A biosimilar is highly similar to the reference product notwithstanding minor differences in clinically active components, and has no clinically meaningful differences from the reference product in terms of safety, purity and potency."); FDA, *supra* note 38 (explains that clinically meaningful difference are generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, as assessment of clinical immunogenicity, and, if needed, additional clinical studies).

93. Currently, the FDA's Purple Book for biologic drugs simply lists approved biological products, their approval dates, any interchangeable or biosimilar licensed by the FDA. However, on January 10th 2019, Senators Susan M. Collins and Tim Kaine introduced *The Biologic Transparency Act (S.659)* which expands the purple book to include both licensed products and patents identified by the biological product license holder that would be infringed if an unauthorized person engaged in "making, using, offering to sell, selling, or importing in the U.S. of the biological product." *See* The Biologic Patent Transparency Act, S. 659, 116th Cong. (1st Sess.) (2019); *see also* Lisa M. Mandrusiak, *Biologic Patent Transparency Act- New Bill Aimed at Biologics*, OBLON (Mar. 12, 2019), https://www.oblon.com/biologic-patent-transparency-act-new-bill-aimed-at-biologics (on file with *The University of the Pacific Law Review*).

94. *See* 42 U.S.C. § 262(l); *see also* Sanya Sukduang & Thomas J. Sullivan, *The Patent Dance*, FINNEGAN, https://www.finnegan.com/en/insights/the-patent-dance-article.html (last visited August 29, 2019) (on file with *The University of the Pacific Law Review*) (42 U.S.C. § 262(l) "contemplates a patent dance consisting of several rounds of disclosure and information exchange" between the biosimilar applicant and the RPS. The authors further distinguish that the BPCIA's elaborate multiple-round litigation "Patent Dance" has a different and perhaps more significant impact on the approval and launch of a follow-on-biologic, than the less-elaborate litigation scheme of the Hatch-Waxman Act).

95. *See* 42 U.S.C. § 262(l)(2) (if it chooses to disclose, the aBLA applicant must disclose its aBLA application and manufacturing process details within 20 days of being accepted by the FDA for review).

96. Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664 (2017).

97. *Id.* at 1664–69, 1673–74 (holding that the §262(l) patent dance is optional, rather than mandatory and the aBLA (biosimilar) applicant can refuse to disclose either or both of its aBLA application and manufacturing process to the RPS (originator biologic)).

infringed" by the applicant, as well as patents that the RPS would be willing to license to the biosimilar applicant.[98] If the aBLA applicant opts out of this portion of the dance, the RPS is limited to filing a declaratory judgement "on any patent that claims the biological product or use of the biological product."[99]

After receiving the patent list, the aBLA applicant has the option to respond in sixty days with its own counter-listing of patents that it reasonably believes could be asserted against the applicant in a patent infringement claim, plus detailed claim by claim statements surrounding any claims for invalidity, unenforceability and non-infringement. The applicant must also respond and address each patent identified by the RPS for potential licensing.[100] After this, both parties have sufficient information to begin negotiating which patents should be the subject of immediate infringement litigation. Within thirty days of this resolution,[101] the RPS must bring an action for each of the agreed-upon patents, thus beginning Phase I of the litigation process.[102] If successful, the RPS is entitled to both equitable and monetary remedies related to the harm created by the applicant's infringing activities.[103]

The aBLA applicant's notification of intended commercial marketing triggers what is typically known as Phase II of the Patent Dance.[104] An applicant may provide this notice prior to FDA approval of the biosimilar or interchangeable

98. 42 U.S.C. §. 262(l)(3)(A). The RPS cannot sue the biosimilar applicant for Patent Act § 271(e) infringement unless it files the patent list within the 60-day statutory period, which may delay the RPS from suing until after the biosimilar reaches the market. Interestingly, the Supreme Court has held that the patent dance is not required, and the aBLA applicant can choose to "opt-out" of the various exchanges. *See* Sandoz v. Amgen, 137 S. Ct. 1664,1669, 1673–74 (2017). Some argue this gives the aBLA applicant "significant control over the scope and timing of litigation." *Id.* at 1673–74. *See, e.g.,* Furrow & Meier, *supra* note 72.

99. 42 U.S.C. § 262§ (l)(9)(C). (Commentators note that based on the statute's plain language, biologics cannot bring declaratory judgements for its manufacturing process patents since it does not claim the "biological product."); *see, e.g.,* Limin Zheng, *The Biosimilar Patent Dance: What Can We Learn from Recent BPCIA Litigation?*, BIOSIMILAR DEVELOPMENT (Mar. 6, 2018), https://www.biosimilardevelopment.com/doc/the-biosimilar-patent-dance-what-we-can-learn-from-recent-bpcia-litigation-0001) (on file with *The University of the Pacific Law Review*) (distinguishing that Genentech cannot bring a declaratory judgment action based on its manufacturing process patents, only its product patents).

100. 42 U.S.C. § 262(l).

101. 42 U.S.C. § 262(l)(5). Technically, if the parties cannot agree on a patent list within fifteen days, the applicant can still inform the RPS of the number of patents it will provide, then the parties exchange respective lists with that – RH. number of patents for immediate litigation. 42 U.S.C. § 262 (l)(5)(B)(ii)(II). If the applicant fails to cite any patents, the RPS can still litigate a since patent.

102. 42 U.S.C. § 262(l)(6). If the RPS gains additional patents or licenses after the initial list exchange, it has 30 days to provide a supplemental list to the applicant. 42 U.S.C. § 262(l)(7).) 42 U.S.C. 262(l)(8).

103. 35 U.S.C. § 271(e). Making using, selling or offering for the infringing product for sale in violation of 35 U.S.C. § 271(a), and excluding actions protected by the Patent Act's 271(e) "safe harbor" provisions.

104. 42 U.S.C. § 262(l)(8)*; see* Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664, 1669, 1673–74 (2017); Amgen v. Apotex Inc., 827 F.3d 1052, 1054–55 (Fed. Cir. 2016) (holding that under the Patent Dance provisions of 42 U.S.C. § 262, an aBLA applicant can provide Phase II notice prior to FDA approval of its drug). Now that an aBLA's can control the 'patent dance' by deciding whether and what to disclose to the RPS, the entire patent dance can occur in what was traditionally Phase II of the dance. Thus, in a single action the aBLA can give both its 180-day commercial marketing notice and notification of its aBLA to the RPS. Now, Phase I and II of the dance would run concurrently and the RPS could assert its entire patent portfolio and the applicant avoids waiting another 180 days before marketing once it obtains FDA approval. *See* Sukduang & Sullivan, *supra* note 94.

product, thereby avoiding an unnecessary 180-day post-approval delay.[105] Both parties can bring patent suits after the Phase II notice; the RPS can sue for listed patents it left out of the Phase I litigation; and the applicant can bring declaratory judgment actions challenging the validity and/or enforceability of listed patents not litigated during Phase I.[106]

On the surface, it appears the Patent Dance gives the aBLA applicant significant control over the pre-market litigation process and provides a level of transparency and pre-market resolution that would incentivize production of both biosimilars and interchangeable products.[107] However, disclosing its aBLA too early in the approval process may place the biosimilar/interchangeable manufacturer at a strategic disadvantage since the RPS obtains critical information about the aBLA applicant's product and manufacturing process early enough to engage in preliminary market-exclusion tactics.[108] Also, the applicant may have time constraints with respect to product launch. Applicants further cannot afford the delays produced by multiple information exchanges and negotiation periods built into this pre-market litigation scheme.[109] Thus, for a variety of reasons, many applicants are choosing to partially or totally opt-out of the Patent Dance.[110] Nevertheless, when parties can agree to efficiently share information, the Patent Dance remains a viable rubric for facilitating innovation and competition.

105. *See* Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664, 1677; Amgen v. Apotex Inc., 827 F.3d 1052, 1054–55 (2016) (the Supreme Court and later the Federal Circuit affirms that under the Patent Dance provisions of 42 U.S.C. § 262, an aBLA applicant can provide Phase II notice prior to FDA approval of its drug).

106. 42 U.S.C. §262(l)(8)(B); *see also* SUKDUANG & SULLIVAN, *supra* note 94; FURROW & MEIER, *supra* note 72.

107. SUKDUANG & SULLIVAN, *supra* note 94; FURROW & MEIER, *supra* note 72; SUKDUANG, *supra* note 86; (noting that views of the current pre-market litigation scheme favors 351(k)/aBLA applicant-particularly after *Sandoz* and its Federal Circuit progeny).

108. SUKDUANG & SULLIVAN, *supra* note 94; CARRIER & MINNITI, *supra* note 14, at 13; Alexej Ladonnikov, Note, *The Biosimilar Patent Dance-If You Don't Dance You're No Friend of Mine*, 35 SANTA CLARA HIGH TECH. L.J. 135 (2018); Price & Rai, *supra* note 11, at 1027.

109. ZHENG, *supra* note 99.

110. CARRIER & MINNITI, *supra* note 14, at 13 (also, some commentators suggest that this choice is driven more by the specific biologic at issue, rather than any characteristics of the applicant itself); *see* SUKDUANG & SULLIVAN, *supra* note 94. Others argue that no single formula determines whether or how far to take the dance. They cite several determining factors, such as: (1) the scope of the RPS's patent portfolio (including the number and type of potential patents at issue); (2) availability of non-infringement and invalidity defenses; (3) the timetable for launch; and (4) the company's resources, including whether incremental wins are needed to raise money to fund litigation. *See* ZHENG, *supra* note 99.

IV. THE FDA'S BIOSIMILARS ACTION PLAN-A STEP IN THE RIGHT DIRECTION TOWARD MAINTAINING BIOLOGIC INNOVATION WHILE INCREASING PATIENT ACCESS TO AFFORDABLE BIOSIMILARS

"The FDA is committed to encouraging innovation and competition among biologics and the development of biosimilars."[111]

Despite its accelerated approval pathway, robust RPS exclusivity period, and pre-market patent litigation framework the BPCIA failed to accelerate biosimilar product development or increase biosimilar accessibility in the United States. Sadly, the U.S. continues to trail Europe in the approval and marketing of biosimilar products.[112] To date, more than 200 originator biologics are currently approved for use and sale in the United States.

[113] Yet, there are only eleven biosimilars on the market in the U.S., available at discounts of only fifteen to thirty-five percent below the originator or "innovator" biologics price.[114] Predictably, biosimilar manufacturers are failing to get traction in the U.S. market because originators can easily match the low discount rates for biosimilars or create payor rebate schemes that insure brand loyalty.[115] In addition, originator biologic manufacturers are notorious for engaging in complex patent litigation tactics and other gaming strategies to further impede biosimilar market entry.[116] In sharp contrast, because of government controlled pricing and more limited patent protection for biologics, there are over fifty-four biosimilars presently marketed in Europe at an average discount of 80%.[117]

To address this impending need to yield tangible results from otherwise fruitless legislation, the FDA created the Biosimilar Action Plan ("BAP"). The BAP was released in July 2018, and it serves as the FDA's most recent attempt to supplement the BPCIA by creating a regulatory framework that seeks to jumpstart

111. Former FDA Commissioner Scott Gottlieb-FDA Biosimilars Action Plan: Balancing Action and Innovation 2 (July 2018).

112. SRAKOCIC, *supra* note 28. Biosimilars have been available in Europe since 2006, with 54 currently available at discounts up to 80% and limiting patent monopolies and government control pricing is frequently cited as the reason Europe has far surpassed the U.S. in this space. The U.S. is described as in the "infancy" stage of biosimilar production—in 2018 the U.S. spent $126 million on biologic drugs, only 2% of it on biosimilars.

113. *See* Kristina M. Lybecker, *The Biologics Revolution in the Production of Drugs*, FRASER INST. (July 2016), https://www.fraserinstitute.org/sites/default/files/biologics-revolution-in-the-production-of-drugs.pdf (on file with *The University of the Pacific Law Review*).

114. *See* SRAKOCIC, *supra* note 28.

115. *Id.*

116. *Id.* ("These discounts are easily matched by originator biologic makers who prefer insurers pay them a smaller piece of the pie than nothing.").

117. *Id.* This success is seen despite the fact that European biologics manufacturers are still known to engage in anticompetitive practices, similar to their U.S. counterparts. *See Report from the European Commission to the Council and the European Parliament* on *Competition Enforcement in the Pharmaceutical Sector* 22 (2009-2017) (noting that companies "attempt to misuse the regulatory system which grants patent exclusivity protection to gain additional protection time.").

biosimilar product development, while preserving the incentive to produce next-generation biologics.[118] In creating the BAP, the FDA mirrored its prior efforts to stimulate a competitive market within the realm of generic drugs. That is, in May 2017, the FDA announced the Drug Competition Action Plan ("DCAP")—a new initiative to facilitate competition for the chemically-synthesized drugs that fall within the purview of the Hatch-Waxman Act.[119] As noted by Former FDA Commissioner Scott Gottlieb, the DCAP was created "to ensure that the competition Congress intended when it passed the Hatch-Waxman Amendments actually occurs."[120]

Likewise, the FDA created the BAP in response to the BPCIA and with a purpose that is otherwise parallel to the underlying goal of the DCAP–to foster pharmaceutical competition.[121] So, it comes as no surprise that the BAP includes four key strategies that are almost identical to the areas of focus within the DCAP.[122] According to the FDA, the BAP's four strategies will foster "a more competitive market . . . while creating greater incentives for sponsors [of biosimilar drug applications] to make the investments required to support future products that deliver greater benefits to patients and public health after statutory exclusivities have expired."[123]

As outlined by the four key strategies of the BAP, the FDA intends to encourage and support the following initiatives in the biosimilar sector:

Improved Efficiency—the first objective focuses on promoting efficiency in the specific areas of product development and FDA approval for biosimilar and interchangeable treatments;

Regulatory Transparency—the second objective focuses on enabling scientific predictability and regulatory transparency for both the biosimilar and

118. *See* U.S. FOOD & DRUG ADMIN., *supra* note 1.

119. *See* FDA, *FDA Tackles Drug Competition to Improve Patient Access*, U.S. FOOD & DRUG ADMIN. (June 27, 2018), https://www.fda.gov/news-events/press-announcements/fda-tackles-drug-competition-improve-patient-access (on file with *The University of the Pacific Law Review*).

120. Sara W. Koblitz & Kurt R. Karst, *FDA's Hatch-Waxman Public Meeting and Progression of the Agency's Drug Competition Action Plan*, HYMAN, PHELPS & MCNAMARA: FDA LAW BLOG (July 19, 2017), http://www.fdalawblog.net/2017/07/fdas-hatch-waxman-public-meeting-and-progression-of-the-agencys-drug-competition-action-plan/ (on file with *The University of the Pacific Law Review*).

121. *See* U.S. FOOD & DRUG ADMIN., *supra* note 1.

122. *Compare id.*, *with* FDA*, FDA Tackles* Drug Competition *to Improve Patient Access*, U.S. FOOD AND DRUG ADMIN. (June 27, 2018), https://www.fda.gov/news-events/press-announcements/fda-tackles-drug-competition-improve-patient-access (on file with *The University of The Pacific Law Review*). The FDA has identified three areas of the DCAP that were designed to increase competition in the pharmaceutical marketplace with the goal of reduced prices and cost-savings for patients. First, the FDA wants to identify instances of "gaming" the regulatory system to delay competition. Second, the FDA wants to identify barriers to entry in the generic market. And third, the FDA will focus on overall efficiency in reviewing ANDAs and maintaining low costs for applicants without lowering standards for approval. These goals are strikingly similar to the four initiatives that the FDA outlined for the BAP such that these four key areas can be viewed as representing existing FDA initiatives, both under the DCAP and under ongoing educational efforts specific to biosimilars.

123. *See* U.S. FOOD & DRUG ADMIN., *supra* note 1.

interchangeable drug applicants and the reference product sponsors;

Targeted Education—the third objective focuses on educating the beneficiaries of biosimilar and interchangeable products (e.g., payors, healthcare providers, pharmacist, and patients) with a goal of increasing the knowledge and awareness surrounding these products; and

Reduced Gaming—the fourth objective focuses on reducing regulatory gaming and other efforts to tactically delay the introduction of biosimilar and interchangeable products into the market.[124]

The BAP also offers a series of "priority deliverables" for each of its key proposals. In essence, the four focal elements of the BAP represent the FDA's projected end goals, while the priority deliverables represent the means for achieving those goals. The BAP deliverables initially focus on providing a hands-on approach that will strategically guide biosimilar applicants to product approval from the product development stage through the application review process itself.[125] Through the use of FDA provided information resources and tools, product sponsors may be able to easily align their development techniques with the criteria required for subsequent product approval.[126] To further bolster this guidance, the FDA is developing biosimilar application templates that outline the necessary information to steer a product toward final approval in the application stage.[127] The increased clarity these templates provide should in return yield a more efficient review process, overall.[128] This move toward efficiency will be partially implemented by creating new positions, and restructuring organizations, to encourage support for biosimilar product approval. A more efficient process further increases communication, consistency, and meaningful assistance throughout the application review.[129]

True competition, however, is not an automatic consequence of merely heightening a sponsor's insight with respect to product approval requirements and review procedures. It also bears on a sponsor's ability to successfully navigate the myriad of regulatory concerns that may arise during both the product development and post-approval phases. For this reason, increased communication is shown to be a recurring theme within the BAP deliverables; one that is manifested to support the BAPs second goal of encouraging regulatory clarity.[130] Here, the FDA aims to both leverage existing guidance documents and engage the public opinion to better

124. *See id.*

125. *See id*.

126. *Id.* Another deliverable under this key area is the development of more information resources and tools "that can assist biosimilar sponsors in developing high quality biosimilar and interchangeable products using state of the art techniques." A specific example given in the BAP is the development of an "index of critical quality attributes for use in comparing proposed biosimilars to certain reference products."

127. *Id.*

128. *Id.*

129. *Id.*

130. *Id.* at 6.

develop their methods for clarifying current biosimilar regulations.[131] These methods cover regulations that pertain to product exclusivity, licensing, interchangeability, and manufacturing, for example.[132]

While the focus on guidance documents clearly highlights the FDA's intention to streamline general communication with the Agency, it also serves as an indicator of the importance of providing increased knowledge within the sphere of biosimilar product development. To this end, the BAP acknowledges that another tangible means to circulate biosimilar-related information is the Purple Book.[133] Since most parties agree the current Purple Book is fairly inefficient in this regard,[134] the BAP proposes an "enhanced Purple Book" that will include more information regarding approved products, withdrawn applications, and exclusivity determinations.[135] In addition to the improved Purple Book, another notable initiative for regulatory clarity is the need to deliver consistency at both domestic and international levels through the use of global partnerships.[136] This includes partnering with European Union countries, as well countries such as Japan and Canada who are demonstrating efficient, safe, and sustainable biosimilar markets.[137] The BAP goes as far to suggests that these partnerships may lend themselves to an appropriate use of foreign licensed comparator products to push

131. *Id.*

132. *Id.*

133. *Id.* (Unlike Hatch Waxman's Orange Book, the BPCIA's Purple Book requires the disclosure of currently approved biological products, including biosimilar and interchangeable products and does not require disclosure of additional information such as related patents, withdrawn applications and exclusivity determinations).

134. Joanne S. Hawana & Muriel M. Liberto, *FDA's New Biosimilar Action Plan Represents the Next Step for Improving Drug Competition*, MINTZ (July 19, 2018), https://www.mintz.com/insights-center/viewpoints/2146/2018-07-fdas-new-biosimilar-action-plan-represents-next-step (on file with *The University of the Pacific Law Review*).

135. U.S. FOOD & DRUG ADMIN., *supra* note 1.

136. U.S. FOOD & DRUG ADMIN., *supra* note 1; *see also* EUROPEAN COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT, COMPETITION ENFORCEMENT IN THE PHARMACEUTICAL SECTOR 3 (2009-2017) (noting the effectiveness of antitrust enforcement to both safeguard innovation and protect against gaming practices such as rebate schemes and misinformation). Although European Countries have taken active efforts to curb anticompetitive behavior, it is also important to note that their more successful biosimilar market is a direct product of its more lenient patent laws and its increased control over pharmaceutical pricing. As the European Commission notes, "while competition law enforcement (antitrust and mergers) contributes to securing access to innovative and affordable medicines for patients and healthcare systems, it does not replace or interfere with the legislative and regulatory measures aimed at ensuring that EU patients benefit from state-of-the-art and affordable medicines and healthcare. Competition law enforcement instead complements the various regulatory systems.").

137. U.S. FOOD & DRUG ADMIN., *supra* note 1 (the FDA also notes that it is exploring data sharing agreements with partner countries. These agreements will provide "real world [global] insights" concerning biosimilar safety and efficacy. When comparing the cost of Consentyx across various nations, the cost ranges from $65K in the U.S., $15 in Italy, and less than $13K in England, which demonstrates the greater control that other countries have over their biologics pricing); *see* Sara Jane Tribble, *Why The U.S. Remains The World's Most Expensive Market For 'Biologic' Drugs*, KAISER HEALTH NEWS (Dec. 20, 2018), https://khn.org/news/u-s-market-for-biologic-drugs-is-most-expensive-in-the-world/ (on file with *The University of The Pacific Law Review*).

approval of new biosimilar applications.[138]

One can easily discern that many of the key areas within the BAP turn on the notions of increased communication and information initiatives, which falls squarely in line with its third, education-centered goal. While the first two elements of the BAP are clearly manufacturer or sponsor oriented, the third element shifts the focus to the consumers of the biosimilar market–namely, payors, clinicians, and patients.[139] The third set of deliverables consider developing effective communications to improve the understanding of biologics for the payors and the individuals responsible for prescribing or receiving the drug.[140] The BPA specifically highlights a number of educational and outreach campaigns already undertaken by the FDA and notes that they will be expanded. Increased consumer knowledge in this area will be particularly beneficial in the efforts to correct the misinformation surrounding both biosimilar and interchangeable products as propelling misguided data into the public domain has now become simply another tactic to game the system.[141]

The BAP recognizes the need to reduce the effect of this technique along with other gaming strategies that are employed by manufacturer to stifle competition in the pharmaceutical market. Accordingly, the final set of deliverables aim to instead promote and support market competition.[142] Specifically, the BAP promises that the FDA "will take action, whenever necessary, to reduce gaming of current FDA requirements, and coordinate with the Federal Trade Commission to address anti-competitive behavior" as well as working with legislators "to close any loopholes that may effectively delay biosimilar competition beyond the exclusivity envisioned by Congress."[143] The presence of vague proposals such as acting "when necessary" demonstrates the FDA's need to be more specific in this regard.

Of the four initiatives outlined by the BAP, the fourth key element that focuses on supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition appears to be the most problematic in terms of the difficulty to assess its likely rate of success. This is in-part because the BAP does not address how the FDA specifically plans to reduce gaming and increase the introduction of approved biosimilars into the market. But in all fairness, the FDA seems to acknowledge its need to provide more clarity in this area.[144] Nonetheless, when viewed in the aggregate, the BAP is certainly a step in the right direction toward maintaining biologic innovation. But standing alone, it is simply not enough to single-handedly fuel a competitive market.

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138. U.S. FOOD & DRUG ADMIN., *supra* note 1.

139. *Id.*

140. *Id.* at 8.

141. *Id.*

142. *Id.*

143. *Id.*

144. *Id.* (acknowledging that the FDA needs to "[c]ontinue to evaluate whether firms are using FDA statutory or regulatory requirements to inappropriately delay approval of biosimilar interchangeable competitors.").

V. THE FDA MUST PARTNER WITH CONGRESS AND OTHER KEY STAKEHOLDERS TO FOSTER COMPETITION AND BUILD A SUSTAINABLE BIOSIMILAR MARKETPLACE FOR PATIENTS IN THE UNITED STATES

"The Biosimilar Action Plan enables a streamlined and simpler biosimilar development process. However, it lacks teeth to create a competitive U.S. biosimilar market . . . the FDA will need to collaborate with other organizations to stimulate biosimilar uptake as many of the steps needed to drive biosimilar adoption are beyond the FDA's purview."[145]

"Because the FDA is not able to address anticompetitive schemes, antitrust law must fill the void."[146]

While the FDA has demonstrated strength in providing adaptive regulation-enhancing regulatory schemes to facilitate innovation and competition, these efforts alone are insufficient to yield the same results in the biosimilar market. This is easily shown when comparing the background of the DCAP and the BAP. Although both the DCAP and BAP were created with similar proposals and a common goal—to ensure that Congress' original intent to generate pharmaceutical competition and innovation is being honored—it is important to note that despite their similarities, these two plans were not created equally. Unlike the BAP, the DCAP was created upon the heels of legislation that had already proven to be successful on its own accord.[147] In particular, the generic competition facilitated by Hatch-Waxman increased the market for generic drugs to at least 88%, and as a result accrued savings of more than one trillion dollars far prior to the creation of DCAP in 2017.[148] In contrast, following the BPCIA, biosimilars still remain a negligible percentage of the market and to date only eleven biosimilars have been approved by the FDA.[149] However, this failure is not the result of a lack of effort as opposed to the fact that effectuating competition goes beyond the FDA's regulatory authority.

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145. HERBERT, PANDYA & SHAHINIAN, *supra* note 3; *see also* Scott Gottlieb, *Statement from FDA Commissioner Scott Gottlieb, M.D., on New Agency Actions to Further Deter 'Gaming' of the Generic Drug Approval Process by the Use of Citizen Petitions*, U.S. FOOD & DRUG ADMIN. (Oct. 2, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-agency-actions-further-deter-gaming-generic-drug (on file with *the University of the Pacific Law Review*) (affirming that the FDA lacks the tools to effectively combat anticompetitive behavior and that these practices are overseen by the FTC).

146. CARRIER & MINNITI, *supra* note 14.

147. *See, e.g.*, GOTTLIEB, *supra* note 145 (affirming that the FDA lacks the tools to effectively combat anticompetitive behavior and that these practices are overseen by the FTC); *see also* CARRIER & MINNITI, *supra* note 14, at 13 (noting that the percentage of prescription drugs that were generics grew from 19% in 1984 to 88% by 2015).

148. CARRIER & MINNITI, *supra* note 14, at 13 (establishing a record of success for the Hatch-Waxman Act prior to the creation of the DCAP).

149. SRAKOCIC, *supra* note 28.

What is within the FDA's regulatory authority is the ability to steer other initiatives by leveraging increased communication, awareness, and education to promote biosimilar approval and introduction into the U.S. market.[150] Despite starting from ground zero, the FDA has established a means to successfully carry-out the majority of the BAP's strategic initiatives.[151] For example, developing application templates will ensure a more efficient accelerated approval process and additional regulatory guidance for stakeholders will clarify regulatory pathway for biosimilars and interchangeable products, thereby satisfying the first and second initiatives of the BAP.[152] The newly updated biosimilar website, along with the Biosimilar Education and Outreach Campaign, demonstrates how the agency is successfully helping professional societies and stakeholders improve their understanding of biosimilars. This, in turn, fosters a positive public-opinion of biosimilar products, thereby countering the host of misinformation currently proffered by originator biologics.[153]

However, given its limited authority, the FDA cannot successfully implement its fourth initiative: reducing regulatory gaming and other efforts to tactically delay the introduction of biosimilar and interchangeable products. Despite an RPS's lasting advantage as the first-market entrant and dominant brand, RPS's are still engaging in activities targeted at delaying or blocking competitor biosimilar market entry.[154] Simply put, the FDA's regulatory powers are insufficient to curb the gaming and other anticompetitive behaviors that most negatively impact access, such as: (1) rebate schemes; (2) pay-for-delay agreements; (3) leveraging innovator patent rights to impede biosimilar market entry (patent thickets); and, (4) other regulatory abuses, such as the filing of fraudulent citizens petitions.[155] Therefore, the FDA must partner with other key stakeholders, such as Congress, the Federal Trade Commission, States, Non-Governmental Organizations, and Payors are therefore crucial to achieving BAP's overarching goal of "promoting competition and affordability [of biosimilars] across the market."[156]

150. *See What We Do*, U.S. FOOD & DRUG ADMIN. (Nov. 10, 2019), https://www.fda.gov/about-fda/what-we-do (on file with *The University of the Pacific Law Review*).

151. *See generally* U.S. FOOD & DRUG ADMIN., *supra* note 1.

152. *Id.*

153. *See* COHEN & MCCABE, *supra* note 35.

154. *See* CARRIER & MINNITI, *supra* note 14, at 13 (discussing that a biologic's brand strength, combined with PBM, physician and patient confidence gives it a lasting competitive advantage and "plays a prominent role in forestalling competition."). In contrast, the biosimilar has the distinct competitive disadvantage of having stakeholders willing to pay a premium for the brand drug, and confronting barriers to entry such as lack of prescriber education and consumer reluctance to switch from the branded biologic.

155. *See, e.g.*, CARRIER & MINNITI, *supra* note 14, at 14 ("Because the FDA is not able to address anticompetitive schemes, antitrust law must fill this void."); *see also* HERBERT, PANDYA & SHAHINIAN, *supra* note 3.

156. GOTTLIEB, *supra* note 4.

VI. REBATE SCHEMES

Rebate Schemes are frequently used as a method to procure or enhance market share for a drug manufacturer. Traditionally, the drug company offers a rebate to Pharmacy Benefits Managers or Group Purchasing Organizations to effectuate preferred status on their formularies.[157] Consumers, participating in the formulary, benefit from the rebate since the preferred drug is typically offered at a lower price than the competing formulary offerings. Unfortunately, Reference Product Sponsors are taking advantage of their dominant market positions to engage in rebate schemes creating an overwhelming preference for originator biologics due to the explicit rebate conditions imposed by sponsors and the overall effect of rebates on drug pricing.[158]

Many Reference Product Sponsors have taken the rebate scheme to monopoly levels by refusing to offer formulary rebates without the PBM's or GPO's agreement to limit its formulary offering to the originator biologic, thereby blocking biosimilar entry.[159] In doing so, these manufacturers have to an extent tied the hands of PBM's and GPO's to force a preferential treatment of their drug at the expense of the biosimilar. Furthermore, when comparing the de minimis 15%–30% discount of biosimilars to a substantial rebate for an originator biologic,[160] the pricing incentive that would otherwise favor biosimilar use, is extinguished. Consequently, while entities such as the U.S. Department of Health and Human Services ("DHHS") minimize the effect of PBM rebates on consumer drug pricing,[161] they fail to consider the use of the scheme to ensure that the comparable biosimilar product will never reach the consumer in the first place. Furthermore, despite the failure to acknowledge their effect, the significance of rebate schemes and their contribution to exorbitant drug pricing is also underscored by more recent legislative efforts.[162] For example, the 2019 bill proposal for the

157. *See, e.g.,* Michael A. Carrier, *Response to Senator Grassley's Questions for the Record. Sen. Jud. Comm. Hearing on "IP and the Price of Prescription Drugs: Balancing Innovation and Competition"* (May 28, 2019).

158. *See* SRAKOCIC, *supra* note 28.

159. *See* Avik Roy, *Biologic Medicine: The Biggest Driver of Rising Drug Prices,* FORBES (Mar. 8, 2019, 8:20 PM), https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/#1fb66d0118b0 (on file with *The University of the Pacific Law Review*).

160. CARRIER & MINNITI, *supra* note 14, at 192–94 (noting that the small discount in comparison to the 90% product discount to generics can be attributed to the high product development cost (upwards of $200 million) and time (8-10 years) its takes to introduce a biosimilar that will limit the number of competing market entrants thereby leading to more modest price reductions).

161. *See* Seth Siber *et al.*, *Pharmaceutical Antitrust Legislation to Watch*, LAW 360 (May 28, 2019, 2:52 PM), https://www.law360.com/articles/1163413/pharmaceutical-antitrust-legislation-to-watch (on file with *The University of the Pacific Law Review*).

162. *See* Daniel Savickas, *FreedomWorks' Bill of the Month for June 2019: The Prescription Drug Price Transparency Act, H.R. 1035*, FREEDOMWORKS' (June 6, 2019), https://www.freedomworks.org/content/freedomworks-bill-month-june-2019-prescription-drug-price-transparency-act-hr-1035 (on file with *The University of the Pacific Law Review*).

Prescription Drug Price Transparency Act, H.R. 1035, attempts to curb this behavior by requiring PBMs to disclose how their prices are determined.[163] Although much like the BAP, the Prescription Drug Transparency Act would entail significant partnerships and converged interest before making a substantial impact.[164]

Regardless of the FDA's applaudable initiative to reduce gaming, on its own, the FDA cannot curtail the use of rebating schemes as a successful gaming tactic that discourages biosimilars as a viable option for patient treatment. Restricting anticompetitive behavior is best handled by Congress, federal courts and agencies such as the FTC and DOJ. Nevertheless, the FDA can educate stakeholders about how these schemes are negatively impacting biosimilar access; and the Federal Trade Commission can work in tandem with the FDA to review and strike rebate agreements that serve to exclude biosimilar market entry.[165]

VII. PATENT THICKETS AND PAY-FOR-DELAY OR (REVERSE SETTLEMENT) AGREEMENTS

Another anticompetitive tactic used by Reference Product Sponsors is the creation of an arsenal of patents or "patent thickets", during the latter stages of its twelve-year exclusivity period. Since the primary role of patent thickets is to block competition, each patent is typically "non-innovative" and covers minor product enhancements that would fail a patent validity challenge. Still, patent thickets are powerful tools to impede market entry since the exorbitant cost of defending numerous patent suits deters competitors from entering the biosimilar market.[166]

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163. H.R. 1035, The Prescription Drug Price Transparency Act, H.R. 1035, 116th Cong. (2019).

164. Stop Significant and Time-wasting Abuse Limiting Legitimate Innovation of New Generics Act, H.R. 2374, 116th Cong. (2019); Preserve Access to Affordable Generics and Biosimilars Act, H.R. 2375, 116th Cong. (2019); CREATES Act, H.R. 2375, H.R. 965, 116th Cong. (2019); Prescription Pricing for the People Act, H.R. 2376, 116th Cong. (2019); *see, e.g.,* CARRIER, *supra* note 157 (proving commentary on these acts). Our next article will address pricing issues and other mechanisms to effectuate access to biosimilars and interchangeable by evaluating the use of "interest convergence", a concept commonly explored by Derrick Bell.

165. Kelly Davio, *Five Things to Know about the Biosimilar Action Plan article,* AJMC (Aug. 10, 2018) https://www.ajmc.com/newsroom/5-things-to-know-about-the-fdas-biosimilar-action-plan (on file with *The University of The Pacific Law Review*); *see also* CARRIER & MINNITI, *supra* note 14, at 14 (evaluating the use of antitrust law to address gaming in the small molecule (traditional) drugs setting and how this framework could enhance the application of antitrust law to address anticompetitive behavior by originator). The authors distinguish that given the emerging nature of the biologic industry, there has been "limited consideration of how antitrust law should apply to biologics. These authors proceed to outline how antitrust law could be used to combat abuse of reverse settlement agreements, the filing of fraudulent citizens petitions, denial of drug samples, disparagement and collusion. *See also* Roy, *supra* note 159 (describing rebate schemes as a "clearly anticompetitive practice which should be litigated by the FTC and banned by Congress.").

166. GAUGH, *supra* note 80; *FDA Approves Adalimumab Biosimilar, Samsung Bioepis' Hadlima,* CTR. FOR BIOSIMILARS (July 23, 2019), https://www.centerforbiosimilars.com/news/fda-approves-adalimumab-biosimilar-samsung-bioepis-hadlima (on file with *The University of the Pacific Law Review*); *see also* Allison Inserro, *Collins, Kaine Seek to Untangle Patent Thickets with Bill Requiring Transparency*, CTR. FOR BIOSIMILARS (Mar. 08, 2019), https://www.centerforbiosimilars.com/news/collins-kaine-seek-to-untangle-patent-thickets-with-bill-r-transparency (on file with *The University of the Pacific Law Review*); Brennan, *supra* note 23; Michelle Chin Kitts*, Biologic Patent Transparency Act Addresses High Prices,* BIOLOGICS & BIOSIMILARS (May 02, 2019),

In the typical reverse settlement, or pay-for-delay arrangement, the originator biologic (RPS) leverages its patent thicket power to settle pending infringement claims in exchange for the biosimilar's agreement to delay market entry of the competitive biosimilar. These delays have the anticompetitive effect of blocking patient access to a more affordable and equally effective treatment option.[167]

AbbVie, the manufacturer of the biologic Humira is frequently cited as the "poster child" of patent thickets. Humira is the world's bestselling medicine[168] and a highly effective biologic for the treatment of psoriatic arthritis, plaque psoriasis and Crohn's Disease. AbbVie's market exclusivity period for this Blockbuster drug was scheduled to end in 2014 and their primary product patent was scheduled to expire in 2016. During the last three years of Humira's market exclusivity period, however, AbbVie created a virtually insurmountable patent thicket by filing more than seventy-five late-stage patents. These patents remain enforceable for periods extending through 2034. Although the FDA has approved two competitive biosimilars for distribution in the U.S., these manufacturers ended up in infringement litigation over AbbVie's late-stage patents for Humira. One biosimilar manufacturer remains in litigation with AbbVie and the other chose to enter into a pay-for-delay agreement where AbbVie agreed to settle its

https://www.lexology.com/library/detail.aspx?g=ac5b4796-8287-45b9-beed-231a72cabfc2 (on file with *The University of the Pacific Law Review*); Affordable Prescriptions for Patients Act , S.1416, 116th Cong. (2019), https://www.congress.gov/bill/116th-congress/senate-bill/1416/text (on file with *The University of the Pacific Law Review*). The Affordable Prescriptions for Patients Act is a bill that proposes to amend the Federal Trade Commission Act to prohibit anticompetitive behaviors by drug product manufacturers, and for other purposes. The bill codifies the definition of patent thickets and classifies it (along with product-hopping) as anticompetitive behaviors within the FTC's enforceability purview.

167. *See, e.g.*, Federal Trade Commission, *Pay-For-Delay: When Drug Companies Agree Not to Compete*, FED. TRADE COMM'N (last visited Sept. 15, 2019), https://www.ftc.gov/news-events/media-resources/mergers-competition/pay-delay (on file with *The University of The Pacific Law Review*). One of the FTC's top priorities in recent years has been to oppose a costly legal tactic that increasingly branded drug manufacturers have been using to stifle competition from lower-cost generic medicines. These drug makers have been able to sidestep competition by offering patent settlements that pay generic companies not to bring lower-cost alternatives to market. These "pay-for-delay" patent settlements effectively block all other generic drug competition for a growing number of branded drugs. According to an FTC study, these anticompetitive deals cost consumers and taxpayers $3.5 billion in higher drug costs every year. Since 2001, the FTC has filed several lawsuits to stop these deals, and it supports legislation to end such "pay-for-delay" settlements. *See also* Emmarie Huetteman, *Klobuchar Want to Stop 'Pay-For-Delay' Deals That Keep Drug Prices High*, KAISER HEALTH NEWS (Apr. 26, 2019), https://khn.org/news/klobuchar-wants-to-stop-pay-for-delay-deals-that-keep-drug-prices-high/ (on file with *The University of The Pacific Law Review*) (describing pay for delay agreements as a practice where "big pharmaceuticals pay off generics to keep the prices and the competition off the market"). Not surprisingly, originator biologics take a different perspective on Pay for Delay Agreements. S*ee, e.g.*, Jonathan Gardner, *Pay-for-Delay Deals Disappearing, FTC Says,* BIOPHARMA DIVE (May 24, 2019), https://www.biopharmadive.com/news/pay-for-delay-deals-disappearing-ftc-says/555546/ (on file with *The University of The Pacific Law Review*) (AbbVie CEO Rick Gonzalez being cited as describing that its reverse settlement agreement with biosimilar Humira product has been "fairly negotiated and does not contain any payments to the biosimilar makers . . . .").

168. HELED, *supra* note 9, at 2 (noting that Humira generated approximately $20 billion in 2018 ($12 B in U.S. and 18B worldwide). Another commentator documents that AbbVie made $36 million/day on Humira sales during the first quarter of 2019.

infringement claims in exchange for the biosimilar postponing U.S. market entry until 2023.[169] While we cite AbbVie as the poster-child for this behavior, numerous brand biologics are leveraging their patent portfolios to create patent thickets and extract similar pay-for-delay settlements.[170]

Monopolistic tactics like patent thickets and pay-for-delay agreements must be curtailed before Congress and the FDA can facilitate continued biologic innovation and patient access to biosimilars. Altering the landscape of existing patent law, is yet another power that goes beyond the FDA's authority. Only Congress can initiate legislation that curbs the creation of patent thickets and prohibits anticompetitive pay-for-delay agreements.[171]

Indeed, the House of Representatives recently passed H.R. 1499, "the Protecting Consumer Access to Generic Drugs Act of 2019," which would prohibit certain pay-for-delay agreements that are used to settle claims of patent infringement between brand-names, generic, or biosimilar drugs relating to the sale of a drug or biological product. The Bill outlines civil penalties for parties that engage in this anticompetitive behavior.[172] The Congressional Budget Office ("CBO") predicts that H.R. 1499 should increase overall accessibility to lower-priced generics or biosimilars covered under pay-for-delay agreements and reduce the average drug price paid by federal health programs that provide drugs or health insurance covering these drugs.[173]

In the regulatory sphere, the FTC has continuously taken an aggressive stance on the presumed anticompetitive effect of reverse-settlement agreements. Historically, courts have failed to agree on whether reverse-settlement agreements are lawful or presumptively anticompetitive. Some courts have found these agreements to be beyond the scope of anticompetitive behavior when the terms of the agreement are consistent with a patents exclusionary period.[174] This disagreement ultimately found itself in the hands of the Supreme Court in *FTC v. Actavi*s. Although the Supreme Court declined to support the FTC's argument that such agreements are presumptively unlawful, it nonetheless affirmed the FTC's ability to subject reverse-settlement agreements to an independent application of antitrust scrutiny. This scrutiny must be considered irrespective of a patent holder's

169. GAUGH, *supra* note 80.

170. *Id.*

171. The Biologic Patent Transparency Act, *supra* note 93; HERBERT, PANDYA & SHAHINIAN, *supra* note 3; Gottlieb, *supra* note 145.

172. *See* Preserve Access to Affordable Generics and Biosimilars Act, H.R. 2375 (May 8, 2019), https://www.cbo.gov/publication/55225 (on file with *The University of the Pacific Law Review*) (providing the April 26, 2019 Congressional Budget Office Cost Estimate for H.R. 1499). The CBO estimates that implementing H.R. 1499 would decrease the deficit by $613 million over the 2019–2020 time frame.

173. *Id.*

174. FTC v. Actavis Inc., 507 U.S. 136, 141 (2013) (noting 11th Circuit precedent which held that "reverse payments did not constitute anticompetitive behavior 'so long as the terms of the settlement remain within the scope of the exclusionary potential of the patent, i.e., do not provide for exclusion going beyond the patent's term or operate to exclude clearly non-infringing products, regardless of whether consideration flowed to the alleged infringer.'").

exclusivity rights because of the potential adverse effect of reverse-settlement agreements on competition and patient access.[175]

Although the traditional framework placed the burden on the small molecule generic drug manufacturer to bring an antitrust claim for the harm caused by anticompetitive settlement agreements, the Administration has empowered the FTC to preemptively address potential antitrust violations surrounding biosimilar and biologic pay-for-delay agreements. The recently enacted Patient Right to Know Drug Prices Act includes provisions requiring drug makers to send details of biosimilar settlement agreements to the FTC for antitrust scrutiny.[176] Under the Act, the FTC can also track biosimilar deals and develop a data record of relevant terms.[177] Commentators predict that the disclosure requirements will increase the number of formal investigations and follow-on enforcement actions by the FTC, thereby reducing pay-for-delay gaming and increasing patient access to lower-priced biosimilars.[178]

VIII. BIOSIMILAR MISINFORMATION AND CITIZENS PETITIONS

While rebate schemes, patent thickets, and pay-for-delay agreements shape the foundation of a solid means to substantially stifle the biosimilar market, they do not capture the full myriad of strategies employed by Reference Product Sponsors to adversely affect the entry of biosimilars into the U.S. biologics market. Other notable tactics within the toolkit for biosimilar deterrence include the strategic use of misinformation to portray biosimilars in a negative fashion and the use of citizens petitions to delay biosimilar market entry. These devices continue to highlight why non-FDA governing bodies must lend a helping hand to truly stimulate innovation and competition within the biosimilar domain.

175. *Id.* at 165; *see also* CARRIER & MINNITI, *supra* note 14, at 168–88 (discussing how traditional drug (small molecule) patent settlement issues were addressed by courts and the FTC and contrasting how reverse settlement agreements might play out under the BPCIA).

176. The Patient Right to Know Drug Prices Act, Pub. L. No. 115–263 (2018). The Patient Right to Know Drug Prices Act became effective in the United States on October 10, 2018. Among other things, it extends to biologic and biosimilar products, a 2003 law requiring drug manufacturers to notify United States antitrust authorities of patent settlement agreements. The idea is to cut down on so-called "pay-for delay" tactics which can slow the introduction of cheaper medicines into the market.

177. The Patient Right to Know Drug Prices Act, Pub. L. No. 115–263 (2018).

178. *See, e.g.*, Andrew Dunn, *Trump Signs Law Allowing FTC to Scrutinize Biosimilar Deals,* BIOPHARMA DIVE (Oct. 10, 2018), https://www.biopharmadive.com/news/trump-white-house-biosimilar-FTC-law/539331/ (on file with *The University of the Pacific Law Review*); Dugie Standeford, *New U.S. Law Requires Reporting of Biologic, Biosimilar "Pay for Delay" Pacts*, IP WATCH (Oct. 18, 2018), https://www.ip-watch.org/2018/10/18/new-us-law-requires-reporting-biologic-biosimilar-pay-delay-pacts/ (on file with *The University of the Pacific Law Review*).

A. Misinformation

Biologics manufacturers are often at the hands of campaigns to intentionally propagate data that is either inaccurate or misleading due to the omission of more positive, accompanying facts. For example, some biologic company websites note that "the FDA requires a biosimilar to be highly similar, but not identical to the [reference product]," but fail to further note the requirement that the biosimilar must have no "clinically meaningful differences from the reference product."[179] In the same vein, biologics manufacturers are also responsible for publicizing an unfounded "danger" associated with switching a patient from an originator biologic to its sister biosimilar product, which is a wholly speculative claim popularly referred to as "non-medical switching."[180]

Despite the lack of data to support many of these misleading claims, influencing the market through misinformation is nonetheless a successful tactic. This is in part possible because all publicly disseminated information, including information grounded in fallacies, has the potential to influence the communal perspective when it is directed at an already skeptical audience, predominately unfamiliar with the true safety and efficacy of biosimilar treatments. To this extent, the FDA has accurately identified the instrumental need for a robust educational campaign to combat these otherwise misheld beliefs. The FDA's current use of its platform to increase the awareness of the rigorous approval process that biosimilars withstand prior to market entry is a critically essential element but still not enough.

The FDA must also use their existing videos and educational materials to emphasize the safety, effectiveness, and overall quality of biosimilar use in comparison to biologics. This information bears a significant importance when attempting to influence the stakeholders responsible for prescribing and approving biosimilars for inclusion within their formulary plans. In this same spirit, biosimilar manufacturers should also advocate on their own behalf as they stand in the best position to directly educate pharmacy benefit managers and group purchasing organization and influence a change in opinion due to their existing relationships with these entities. Public educational efforts may be further supported by other non-governmental organizations, such as the Biosimilars Council, who possess the ability and resources to similarly educate their respective audiences and positively influence the public opinion, as a result.[181]

Here again, education represents only one piece in an ever-complex puzzle to

179. 42 U.S.C. § 262(i)(2) (a biosimilar is "highly similar to the reference product notwithstanding minor differences in clinically active components and has no 'clinically meaningful differences from the reference product in terms of safety, purity and potency.'"). The FDA website section on biosimilar and interchangeable products explains that clinically meaningful differences are generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, as assessment of clinical immunogenicity, and, if needed, additional clinical studies. *See also* COHEN & MCCABE, *supra* note 35.

180. GAUGH, *supra* note 80.

181. *Id.*

address competitive gaming in the biosimilar field. A puzzle that the FDA simply cannot solve on its own. For example, while it is completely within the FDA's purview to educate the public and encourage others to do the same to counteract the effect of misinformation, the FDA lacks the power to force biologic manufacturers to provide complete and accurate data through their respective public informational channels.[182] However, by encouraging the FTC to classify this conduct as prohibited antitrust behavior, an RPS would be more inclined to put forth an honest effort when developing its otherwise skewed marketing campaigns. Through the continual misrepresentation of information, biologic manufacturers have been able to indirectly impact the willingness of the consumer industry to wholeheartedly adopt the notion that biosimilars are a safe and more affordable alternative to originator biologic treatments.[183] To this end, the FDA must engage the FTC, the courts, and non-governmental organizations to collectively contest the routinely disseminated misinformation and fuel the positive shift in public opinion that is necessary to stimulate an otherwise compromised biosimilar market.

IX. CITIZENS PETITIONS

The Citizens Petition is another type of eleventh-hour misinformation tactic commonly used to thwart the market-entry of biosimilars in the United States. Under the FDA's regulatory provisions, "interested person" can use the Citizen Petition to challenge the safety or efficacy of any drug that the FDA is currently considering for approval.[184] The policy behind the Citizen Petition is to ensure that drugs entering the U.S. market possess the evaluated standard of safety and efficacy and that the FDA clarifies any ambiguity surrounding licensed drug products. Despite the potential for these petitions to raise relevant concerns, they place a heavy burden on FDA resources and negatively impact the overall efficiency of the drug approval process as the FDA must individually evaluate the merits of each petition.[185]

As a result, originator drug manufacturers, including biologics, have abused this process by filing frivolous petitions in an attempt to artificially extend their market exclusivity. For example, in the small molecule setting, ViroPharma was cited by the FTC as the first drug manufacturer to misuse citizen petitions to delay generic market entry. Specifically, ViroPharma submitted forty-six FDA filings to challenge a single generic drug, and twenty-four of these filings were citizen

182. The United States Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C § 9 (1938).

183. *See also* COHEN & MCCABE, *supra* note 35.

184. More specifically, 21 C.F.R. §§ 10.25 and 10.30 provide that the interested person or citizen can request that the FDA "issue, amend, or revoke a regulation or order" or "take or refrain from taking any other form of administrative action" based on the lack of safety or effectiveness validated through the Petition and FDA review.

185. *See* GOTTLIEB, *supra* note 145.

petitions, which the FTC described as "repetitive, serial, and meritless filings [that] lacked any supporting clinical data." Despite the FTC's initiative to call out this abusive behavior by challenging the underlying petitions, the damage was already done. ViroPharma's tactic successfully delayed market entry with an accompanying price tag that reached upward of hundreds of millions of dollars.[186]

To date, originator biologics have utilized Citizen Petitions to challenge the FDA's guidance regarding biosimilars and the BPCIA.[187] Before Congress had time to enact the BPCIA, Genentech filed a Citizen Petition requesting that the FDA: (1) stop the publication of their draft guidance document establishing standards for biosimilars (described in 2004 as "generic" biotechnology-derived products), and (2) refrain from approving such products since formulation and implementation of an abbreviated pathway for biosimilars was not supported by current science because originator biologics and biosimilars are manufactured using completely different, complex manufacturing processes. Genentech further stressed that such "guidance documents" would rely on originator's commercial data and information, in violation of protection provided under Section 505(b)(2) of the FDCA, the Trade Secrets Act, and the U.S. Constitution. The FDA denied Genentech's petition, finding that the guidance would not violate an originator biologic's confidential information and that the FDA did not impermissibly use or rely on such information when developing the guidelines.[188]

More recently, several biologics have filed Citizen Petitions addressing legal issues relating to the BPCIA, rather than challenging the safety and efficacy of specific biosimilars. For example, on April 12, 2012, Abbott Laboratories (now AbbVie) filed a petition arguing that the use of its proprietary data during any FDA abbreviated approval process for a Humira biosimilar constitutes an unconstitutional taking of the company's intellectual property.[189] So, although some commentators suggest that Citizens Petitions will not be as aggressively abused as they are in the generic drug setting, they still have a potential to pose a concern in the biologic domain.[190]

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186. Michael A. Carrier, *Five Actions to Stop Citizen Petition Abuse,* 118 COLUM. L. REV. 81, 83–84 (2018), https://columbialawreview.org/wp-content/uploads/2018/03/Carrier_Five-Actions-To-Stop-Citizen-Petition-Abuse.pdf (on file with *The University of the Pacific Law Review*).

187. *See generally What Arguments Were Made in Genentech's Citizen Petition on Biosimilars?*, BIOTECHNOLOGY INNOVATION ORG., https://www.bio.org/articles/what-arguments-were-made-genentech%E2%80%99s-citizen-petition-biosimilars (last visited Aug. 8, 2019) (on file with *The University of the Pacific Law Review*).

188. *Id.*

189. *See* Courtenay C. Brinckerhoff, *Will the Biologic Patent Transparency Act Shrink The Biosimilar Patent Dance Floor?*, FOLEY & LARDNER LLP: INSIGHTS BLOG (May 7, 2019), https://www.foley.com/en/insights/publications/2019/05/will-bpta-shrink-patent-dance (on file with *The University of the Pacific Law Review*); Carrier & Minniti, *supra* note 14, at 12 55–58 (2018). The authors cite additional Citizen's Petitions filed by Amgen (filing a Citizen's petition requesting that the FDA force biosimilars to certify that they will engage in Phase I of the Patent Dance). Interestingly, biologics who also market biosimilar are filing petitions advocating for biosimilar friendly rules (Novartis petition) and more favorable biosimilar friendly guidance concerning biosimilar naming and other issues (Pfizer).

190. CARRIER & MINNITI, *supra* note 14, at 58.

Unlike the other gaming strategies discussed, the FDA has a higher degree of control over Citizen Petitions because it is the agency responsible for evaluating each petition on its merits.[191] The FDA has taken a firm stance on its desire to curb the fraudulent and deceptive use of citizen petitions to delay market entry,[192] which includes continuing its current efforts to ensure these petitions are reviewed in a manner that will not further delay review and approval of the targeted products.[193] Additionally, the FDA has identified the need to conduct preliminary reviews of all citizen petitions to determine whether the petition holds genuine merit or whether it is the guise of an attempt to thwart the biosimilar market.[194] Some commentators have suggested that the FDA should presume that petitions filed within a specific time period are for an anticompetitive purpose, in which the petitioner possesses the burden to rebut this presumption.[195] The FDA has further suggested that "public shaming" may be another method to deter manufacturer gaming tactics.[196] This may occur in the form of reporting the abusive behavior to Congress, the FTC, and the public at-large.[197] The task of reporting this behavior to the FTC will be particularly useful as it aligns with the FTCs current mission to preemptively challenge these mechanisms.[198]

X. THE BIOLOGIC PATENT TRANSPARENCY ACT

One theme that is constantly echoed throughout the concerted efforts to push toward increased biologics innovation and access is the need for transparency with respect to originator biologics patents and manufacturing processes. On this front, the recently proposed Biologic Patent Transparency Act provides an example of how Congress can work in tandem with the FDA and other stakeholders to enable a sense of clarity that will foster innovation and build a competitive and sustainable biosimilar marketplace for patients.[199] Such partnerships may yield a well-oiled

191. *See* GOTTLIEB, *supra* note 145.

192. *Id.* ("[The FDA] will not shy away from calling out instances where we believe brand firms may be leveraging tools intended to serve a useful purpose to instead thwart competition that can drive down prices for patients. We're taking the abuse of this system seriously.").

193. *Id.*

194. *Id.*

195. Patrick C. Gallagher, *Maintaining the Balance Between Encouraging Innovation and Promoting Access to Affordable Medications: FDA Looks at Improving Implementation of the Hatch-Waxman Amendments*, FOOD & DRUG L. INST. https://www.fdli.org/2017/07/fda-looks-improving-implementation-hatch-waxman-amendments/ (last visited Sept. 15, 2019) (on file with *The University of the Pacific Law Review*) ("Such an approach would place the burden on the party filing the Citizen Petition to justify the concerns being raised before the acceptance of a Citizen Petition that might delay generic market entry.").

196. GOTTLIEB, *supra* note 145.

197. *Id.*

198. *See* SIBER, *supra* note 161 (discussing H.R. 2374, the Stop STALLING Act, which give the FTC a greater degree of authority to bring suits against anticompetitive behavior based on citizens petitions).

199. Although the consensus focuses on the need to leverage a partnership with Congress to stimulate the biosimilar market, some commentators note that partnerships with local, state governments are equally important.

machine to boost innovation where non-government organizations advocate for balanced and clear statutes, Congress legislates to solidify patent disclosure requirements, the FDA provides a consolidated, easily accessible platform for these disclosures through the Purple Book, and biologics and biosimilar manufacturers amicably comply with these requirements.[200] In return, the U.S. biologics market will ultimately begin to reflect the reduce patient drug prices that have been long sought after.

While Congress should be commended for its early legislative initiatives that sought to create a more competitive biologics market, one common criticism of the BPCIA is that it established a complex framework for resolving patent disputes that in fact works against this goal.[201] That is, the patent dance has a potential to tip the scales in favor of an already advantaged RPS by graciously offering them a biosimilar applicant's product and manufacturing information, which can be leveraged to engage in preliminary market-exclusion tactics.[202] Therefore, it comes as no surprise that many biosimilar manufacturers opt out of this completely optional requirement. The Biologic Patent Transparency Act represents Congress's effort to correct this imbalance through the forced disclosure of potentially infringeable patents, similar to what is achieved by the Hatch-Waxman Act.

To be specific, the Biologic Patent Transparency Act aims to improve transparency by extending the disclosure requirements for the already-existing "Purple Book," and formatting it into a searchable database.[203] While the BAP also proposes an improved Purple Book that will include more information regarding approved products, withdrawn applications, and exclusivity determinations, the Biologic Patent Transparency Act goes one step further to mandatorily require the disclosure of potentially infringeable patents associated with its approved biologic

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See Nicolas Arkells, *Why Biosimilar Companies Should Pay More Attention to U.S. State Governments*, BIOSIMILAR DEV. (May 1, 2018), https://www.biosimilardevelopment.com/doc/why-biosimilar-companies-should-pay-more-attention-to-u-s-state-governments-0001 (on file with *The University of the Pacific Law Review*).

200. For example, the Congressional Research Service (CRS) creates an annual report that outlines major policy issues to provide Congress with the highest quality of research and analytics. .CRS service provides "expertise in every area of interest to Congress: American law, domestic policy, foreign affairs, government, and science and industry." In the pharmaceutical space, CRS provides Congress with analysis of prescription drug development, distribution, coverage and spending issues. In 2018, the administration released "American Patients First" blueprint, which provides strategies to reduce drug prices. Through this information, Congress gained the needed expertise to analyze potential reform of the Public Health Service Act Section 340B drug pricing program that increased the manufacturer discount on certain brand-name drugs. The service also assisted Congress with proposals to increase generic drug development and approval, promote price transparency (including disclosure in advertisements) and assessment of the feasibility of drug importation. *See* Congress Research Service, CRS Annual Report Fiscal Year 2018 (Jan. 2019), https://fas.org/sgp/crs/crs18.pdf (on file with *The University of the Pacific Law Review*). Since CRS reports are made public, other stakeholders such as NGO's, States and PBM's can utilize this information to create and promote their own pricing policies.

201. BRINCKERHOFF, *supra* note 189.

202. SUKDUANG & SULLIVAN, *supra* note 94; CARRIER & MINNITI, *supra* note 14, at 8; LADONNIKOV, *supra* note 10; PRICE & RAI, *supra* note 11, at 1027.

203. The Biologic Patent Transparency Act, *supra* note 93.

products, along with other information related to the licensing and potential biosimilarity and interchangeability of those products.[204]

Although these disclosures requirements are imposed on both originator biologics and biosimilar applicants alike, reference product sponsors may argue that this process is unfairly premature on their behalf because the list of related patents must be disclosed within thirty-days of approval and also updated to include any newly approved patents within the same thirty-day period. This disclosure is required long before the biosimilar applicants are forced to do the same.[205] In some minds, this disadvantage supports the argument for the patent dance to be a mandatory requirement. The Biosimilar Patent Transparency Act has also been viewed as being unnecessarily broad because the patent disclosure may extend to a biologics composition, method of use, and manufacturing process, which is far more information than is required by Hatch-Waxman.[206]

Another problem with the Act in its current form is that originator biologics typically file their patent applications well before clinical trials begin and the final product will likely undergo alterations before obtaining final FDA approval.[207] This results in approved biologic products and associated processes that only partially overlap with the original patent disclosure.[208] Thus, a biosimilar cannot fully rely on patent disclosures made by the RPS within thirty days of filing its application to obtain the complete array of biologic product or process information needed to establish biosimilarity or interchangeability.[209] We advocate for amending the current version of the Transparency Act to mandate that upon FDA approval, the originator biologic must supplement existing patent disclosures with any modifications or additional information necessary to produce biosimilar or interchangeable products. As noted by commentators prior to the release of this Bill, "this ensures that competitors could actually make a biosimilar once the patent expired."[210]

To further complicate matters, the disclosure of the biologics manufacturing process is typically the subject of coveted trade secrets, rather than patents.[211] Thus, the most essential information necessary to establish biosimilarity or interchangeability cannot be obtained by making RPS patents more accessible

204. *Id.*

205. *Id.*; *see also* MANDRUSIAK, *supra* note 93 (noting that "[T]he bill would apply retroactively: within 30 days of enactment, the holders of previously-approved biologic products must submit patent lists.").

206. *See* Ryan Davis, *Senate Patent Bill To Boost Biosimilars Needs Work, Attys Say*, LAW 360 (Mar. 8, 2019), https://www.law360.com/articles/1135931/senate-patent-bill-to-boost-biosimilars-needs-work-attys-say (on file with *The University of the Pacific Law Review*).

207. PRICE & RAI, *supra* note 11, at 1050–51 (discussing Enbrel's principal patent, which exemplifies the issue through its disclosure of at least 20 different ways to create a patented protein, and it further notes that while the patent does describe specific examples they are only "exemplary" rather than the best most).

208. *Id.* at 1050–51.

209. *Id.*

210. *Id.* at 1052.

211. *Id.* at 1046.

during the 351(a) biologic approval process.[212] Even the FDA is prohibited from releasing to the public information "concerning any method or process which as a trade secret is entitled to protection." [213] Consequently, to gain FDA approval, biosimilar manufacturers must make several attempts to reverse engineer the originator biologic's manufacturing process, which can result in clinical trial costs ranging from $100–$250 million.[214] Once again, we advocate amending the proposed Bill to require originator biologics to disclose, in addition to filed patents, all proprietary and non-proprietary information relating to the product and associated manufacturing processes.[215]

XI. CONCLUSION

The BAP's four key regulatory strategies and their related product deliverables are "aimed at promoting competition and affordability [of biosimilars] in the United States." Through this initiative the FDA can continue its positive impact by enhancing informational resources and further streamlining the FDA approval process for biosimilars. However, when considering the FDA's insufficient bandwidth to reduce anticompetitive behavior and getting competitively-priced biosimilars into the market, the FDA must work in tandem with key stakeholders to curb the misinformation, litigation, gaming and other pricing tactics used by originator biologic manufacturers to impede biosimilar market entry. Collective efforts with entities such as Congress, State Governments, Payors, and NGO's can create a force of statutory, regulatory, pricing and data access platforms that will ignite a positive spark in the U.S. biosimilar market, and simultaneously preserve the incentive to produce next-generation biologics.

212. *Id.* at 1048–49 (noting the 1994 Carnegie Mellon survey, as well as 2008 NSF survey, both showing that the BioPharma significantly relies on trade secrecy, particularly for their manufacturing processes); CARRIER & MINNITI, *supra* note 14, at 8.

213. 21 U.S.C. § 331(j) (2010).

214. Price & Rai, *supra* note 11, at 1049–50. The authors conclude that this arrangement creates a "significant barrier to entry" for biosimilars and interchangeables, barriers that will threaten true generic competition in the foreseeable future.

215. Price & Rai, *supra* note 11, at 1049–53, 1053–56. The author also suggest that the FDA could play a role in mandating disclosure of proprietary and non-proprietary information, in which originator biologics would be required to disclose precise and enabling manufacturing methods as a condition of FDA approval. The authors suggest extending the exclusivity period as an incentive for this disclosure. We agree with the authors that perhaps the ideal framework involves a collaborative research and development efforts.