2020

Regulatory Malfunctions in the Drug Patent Ecosystem

Ana Santos Rutschman

REGULATORY MALFUNCTIONS IN THE DRUG PATENT ECOSYSTEM

Ana Santos Rutschman*

Patent protection for several of the world's best-selling and most promising drugs—biologics—has begun waning. Over the next few years, many other drugs in this category will lose critical patent protection. In principle, this should open the United States market to competition, as more manufacturers are now able to produce relatively cheaper versions of these expensive drugs, known as biosimilars. That, however, has not been the case. This Article examines this problem in the context of the articulation between anticompetitive behaviors and regulatory interventions in the biopharmaceutical arena, and argues for a novel solution: a timelier response provided by the U.S. Food and Drug Administration (FDA) in the form of license revocation when follow-on innovators fail to compete.

In one significant case, the FDA approved several biosimilar versions from different manufacturers that would in principle compete with the biologic drug Humira—the largest-grossing drug in the United States and worldwide—but the manufacturer of Humira entered into multiple agreements with biosimilar manufacturers to keep the drug out of the United States market until 2023, while making it available elsewhere from 2018 onwards.

An abundant stream of scholarship has examined the relationship between pharmaceutical markets and antitrust mechanisms to curb anticompetitive behaviors. This Article moves the debate in a new direction. Because antitrust responses generally face a time lag, the Article posits that an additional regulatory intervention is needed outside antitrust law, and it argues that the FDA is institutionally well placed to provide a first-line checkpoint for anticompetitive agreements that result in non-commercialization of approved drugs. While novel, this proposal incorporates a solution that has been hiding in plain sight: the FDA regulatory framework allows the Agency to revoke licenses under certain circumstances, including some forms of inaction on the part of the licensee. This Article shows that the FDA not only has the authority, but also the statutory obligation, to revoke the licenses of biosimilar manufacturers who deliberately fail to bring their products to market within a reasonable period of time.

Many of the biologics slated to lose patent protection in the first half of the 2020s are routinely used in the treatment of some of the most challenging medical conditions of our time, including certain cancers and auto-immune diseases. At a time when concerns over drug prices are at the forefront of political and social debates, finding ways to instill competition into post-patent markets remains a crucial task. The solution put forth in this Article furthers the interests of

* Assistant Professor of Law, Saint Louis University School of Law. S.J.D., LL.M., Duke Law School. For helpful insights and comments, I would like to thank Michael Carrier, Jorge Contreras, Leslie Francis, Rob Gatter, Hank Greeley, Mark Lemley, Nicholson Price, Jerome Reichman, Rachel Sachs, Charlotte Tschider and Spencer Waller. I am also grateful to the readers at the Biosciences Workshop at Stanford Law School, and the participants at the 2019 Innovation, Justice and Globalization Conference at Harvard Law School, the Center for Law & the Biosciences Colloquium at the University of Utah S.J. Quinney College of Law, the Regulation and Innovation in the Bio Sciences Workshop at Washington University School of Law, and the Wiet Life Sciences Conference at Loyola University Chicago School of Law. Thank you also to Hannah Brennan for invaluable research assistance.

different parties, as it clears the pathway for motivated biosimilar manufacturers to bring their products to a profitable market while bringing down overall costs for health systems and, in particular, for patients in need of extremely expensive pharmaceuticals.

TABLE OF CONTENTS

INTRODUCTION

Imagine a patient in need of a pharmaceutical drug with an annual price tag of $40,000–$50,000. This drug is a biologic, a category of structurally complex drugs targeting a broad range of serious medical conditions, from certain cancers to inflammatory diseases such as rheumatoid arthritis and Crohn's disease.[1] As dozens of patents begin expiring—including the most relevant patent, covering the drug's composition—competitors gear up to manufacture versions of the drug, which are subsequently reviewed and approved by the competent regulatory agency and may therefore enter the market.

Now consider a possible bifurcation in this story. In one market, the follow-on versions[2] of the biologic become commercially available shortly after the composition patent expires. Prices go down by roughly 25%. In some places within this market, the savings to the patient are as modest as 10%, while in others they reach up to 80%, even though the latter number occurs very infrequently.[3] Even if annual savings are on the lower end of the spectrum at 10%, our hypothetical patient is still spending $4,000 to $5,000 less than before patent expiration. If savings reach the average 25%, our patient saves between $10,000 and $12,500. In the rare scenario of an 80% reduction, savings can reach between $32,000 and $40,000.

In a different market with similar economic characteristics, follow-on versions of the biologic are also developed, and several receive approval from the regulatory agency in charge of reviewing pharmaceutical products, but none comes to market. Instead, and amidst patent litigation concerning the secondary patents associated with the reference biologic drug, all the manufacturers of the follow-on products enter into agreements with the manufacturer of the biologic. All patent litigation comes to an end, in exchange for access to a foreign market. The manufacturers of the follow-on biologic start selling their product abroad under a multi-competitor regime. In the domestic market, with only the reference biologic available to patients, prices do not go down. In fact, the single manufacturer on the market promptly raises the price of the biologic after the expiration of the composition patent by around 10%, as it had been doing before patent expiration. Because each agreement lasts between four to five years, our patient will likely have no access to a cheaper drug for a protracted period of time, even though it is available to patients in a similar market.

As the reader might have guessed, our patient is not so hypothetical. The market in which no competition occurs is the United States. The foreign market is Europe. The biopharmaceutical drug is Humira, the world's best-selling drug since 2012. While follow-on versions of Humira—

[1] The Public Health Service Act, which regulates the approval of biologics, biosimilars and interchangeable drugs, defines "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." See 42 U.S.C. § 262(i)(1).

[2] Follow-on products are cheaper versions of previously approved pharmaceutical drugs, as is the case of generics. In the field of biologics, their follow-on counterparts are known as biosimilars. See *infra*, Part II. See also 42 U.S.C. § 262(i)(2) and § 262(i)(3) (defining biosimilars and interchangeable products).

[3] *Infra*, Part III.

called biosimilars—have been entering the European market since 2018,[4] no such thing has happened west of the Atlantic. The same manufacturers that commercialize biosimilars to Humira in Europe have agreed not to sell them in the United States,[5] even though Humira's composition patent expired December 31, 2016 in the United States, and the Food and Drug Administration (FDA) approved the first of these biosimilars in September 2016.[6] Per the terms of the agreements, biosimilars to Humira will not be commercially available in the United States until 2023.[7] In exchange, the manufacturer of Humira has ended all litigation—and threat thereof—involving Humira's vast secondary patent estate, in which several patents have already been successfully challenged and invalidated by biosimilar companies.[8]

Biologics like Humira consist of large, structurally complex molecules, as opposed to small-molecule drugs, which still form the bulk of pharmaceutical drugs available to patients.[9] They are made of living organisms[10] and "produced by biotechnology methods and other cutting-edge technologies."[11] Their complexity renders them difficult and expensive to develop, as well as hard to replicate.[12] Importantly, many biologics are among the most promising and needed biopharmaceutical products around the world.[13] By extension, they are also extremely pricey and profitable.[14] While Humira and other biologics like breast cancer-treating Herceptin have a price tag between $50,000 and $70,000,[15] a wave of newer-generation biologics recently entered the United States market at prices in the six and seven digits.[16]

---

[4] See Dominic Tyer; *2018 in Review: Humira Biosimilars Arrive in Europe*, PHARMAPHORUM (Dec. 20, 2018); Arlene Weintraub; *Humira Biosimilars Catch Fire in Europe and Could Take Half the Market in a Year*, FIERCEPHARMA (Jan. 25, 2019).

[5] See Andrew Dunn, *With Boehringer Settlement, AbbVie Completes Humira Sweep*, BIOPHARMA DIVE (2019).

[6] AMGEN, *FDA Approves Amgen's AMJEVITA™ (Adalimumab-Atto) for Treatment of Seven Inflammatory Diseases* (Sept. 23, 2016). See also Appendix 2 (listing all FDA approvals and pay-for-delay settlements involving biosimilars to Humira in the United States).

[7] See e.g. Suzanne Elvidge, *AbbVie Nets 7th Humira Biosimilar Deal, Pushing Pfizer Entry to 2023*, BIOPHARMA DIVE (Dec. 5, 2018); Eric Sagonowsky, *Boehringer Buckles in AbbVie Patent Fight, Saving Humira from Biosims Until 2023*, FIERCEPHARMA (May 14, 2019).

[8] See e.g. Ned Pagliarulo, *Coherus Wins Humira Patent Ruling, Chipping Away at AbbVie's Defenses*, FIERCEPHARMA (May 17, 2017); Jan Wolfe, *PTAB Sides with Boehringer in Challenge to Humira Patent*, REUTERS (Jul. 7, 2017).

[9] See e.g. W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation* [hereinafter *Manufacturing Barriers*], 101 IOWA L. REV. 1023, 1026 (2016).

[10] See Ian Haydon, *Biologics: The Pricey Drugs Transforming Medicine*, The Conversation (July 26, 2017).

[11] U.S. FOOD & DRUG ADMIN., *What Are "Biologics?" Questions and Answers* [hereinafter *What Are "Biologics?"*], (2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.

[12] See Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1, 3 (2018).

[13] See generally Haydon, *Biologics: The Pricey Drugs Transforming Medicine*, *supra* note 10. See also *infra*, note 355 and accompanying text.

[14] See *infra*, Part III.A.

[15] *Infra*, note 171 and accompanying text.

[16] See e.g. Denise Roland, *At $2 Million, New Novartis Drug is Priciest Ever*, WALL ST. J. (May 24, 2019) (reporting FDA approval of Zolgensma, a gene therapy targeting a rare genetic condition known as spinal muscular atrophy).

Agreements between pharmaceutical companies seeking to delay market entrance of profitable drugs are not new. The phenomenon first appeared in the context of small-molecule drugs[17] and became known as "reverse payment" or "pay-for-delay" settlements.[18] These agreements first came to the attention of the Federal Trade Commission (FTC) in 2000,[19] and in 2013 the Supreme Court ruled in *Actavis* that pay-for-delay was subject antitrust scrutiny.[20]

The trigger for these agreements is often the impending expiration of the core patent or patents covering a financially profitable drug. Unlike conventional drugs, which on average were protected by fewer than five patents,[21] biologics are protected by large patent estates.[22] The manufacturer of Humira, for instance, applied for over 200 patents in the United States, and was granted over 100.[23] Typically, as the most relevant patents covering a drug begin expiring—or are invalidated—follow-on competitors start taking steps to produce and obtain FDA approval to market a generic version (in the case of small-molecule drugs) or a biosimilar version (in the case of biologics)[24] of the reference product. Twice before, around 2001 and 2011, several pharmaceutical products faced en masse patent expirations occurring within a short period of time.[25] This thinning out of patent protection is often referred to as a "patent cliff," particularly within the pharmaceutical industry.[26]

The 2001 and 2011 waves of patent expirations affected best-selling drugs like Prozac and Lipitor,[27] whose revenue streams plummeted as soon as generic manufacturers were able to bring their products to market.[28] Confronted with the prospect of sudden and sharply declining revenue,

---

[17] This category includes drugs like aspirin, Prozac and Lipitor (a drug treating high cholesterol levels).

[18] See e.g. Carrier & Minniti, *Biologics: The New Antitrust Frontier*, *supra* note 12 at 1.

[19] *Infra*, note 315.

[20] *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013). *Infra*, Part III.B.

[21] See *infra*, note 63 and accompanying text.

[22] *Infra*, Part III.A (describing how the average number of patents covering a single drug has climbed from the single digits to the dozens and, in some cases, to the hundreds).

[23] *Infra*, Part III.A (presenting a case study on the Humira). See also Appendix 1 (describing the current Humira patent estate).

[24] In addition to biosimilars, follow-on biologics also encompass "interchangeable products." See 42 U.S.C. § 262(i)(3). To date, however, no interchangeable product has gained FDA approval. See also generally Yaniv Heled, *Follow-On Biologics Are Set Up to Fail*, 2018 U. ILL. L. REV. ONLINE 113 (2018) (describing systemic flaws in the regulatory pathway for the review and approval of follow-on biologics).

[25] *Infra*, Part I.B.

[26] As seen in Part I, thinning out of patent protection should in principle enable follow-on competitors to enter the market. However, gamesmanship of regulatory regimes can be used to artificially keep competitors at bay, as detailed in Part III. In some areas outside of legal scholarship, and particularly among industry commentators, the expression "patent cliff" is often used to emphasize the economic loss to patent holders brought about by the expiration of core patents on a drug, an emphasis not adopted here. See e.g. Elizabeth Doughman, *Impending Patent Cliff Threatens Billions of Global Prescription Drug Sales*, Pharma Processing World, https://www.pharmaceuticalprocessingworld.com/impending-patent-cliff-threatens-billions-of-global-prescription-drug-sales/ (last accessed Jan. 9, 2020).

[27] See Part I.B.1 (describing the first wave of patent expirations across the pharmaceutical industry) and Part I.B.2 (describing the second wave).

[28] *Id., ib.* Notice that post-patent decline of revenue is a consequence of the mechanics of patent law, and a natural consequence of loss of market exclusivity. Gamesmanship of regulatory regimes, however, has enabled some players in the pharmaceutical patent ecosystem to artificially prolong market exclusivity by amassing abnormally

innovator companies began entering into pay-for-delay agreements with follow-on manufacturers, a scenario that is virtually identical to the hypothetical presented above, as well as to the agreements between the manufacturer of Humira and the biosimilar manufacturers preparing to take advantage of the thinning out of Humira's patent estate.

There is, however, an important distinction between the previous instances of temporally concentrated patent expirations across the pharmaceutical industry and the landscape Humira is a part of. The 2001 and 2011 waves of patent expirations affected small-molecule drugs. The ongoing wave of patent expirations is the first to affect biologics. Recall that these are not only the most cutting-edge products available to patients, but they also treat especially serious medical conditions. The social and economic impact of the ongoing wave is markedly different from previous waves. The consequences of pay-for-delay agreements involving biologics to the health of individuals and to health systems as a whole is of a much larger magnitude than before.[29] Moreover, the regulatory pathway that enables the approval and commercialization of biosimilars is relatively recent and, according to several commentators, poorly designed and prone to gaming.[30] These combined characteristics should make regulators, policy makers, interest groups and legal commentators be particularly concerned with anticompetitive behaviors involving biologic products.

Yet our hypothetical scenario is not hypothetical at all. The first manifestations of pay-for-delay in the context of biologics occurred in 2016. Under *Actavis*, they should be subject to antitrust scrutiny.[31] But it was not until 2019 that the first lawsuits were brought against the manufacturer of Humira and the biosimilar manufacturers potentially competing with it.[32] Unless a legal intervention changes this landscape, there will be no biosimilar competition in the United States until 2023—five years after the first biosimilar to Humira entered the European market, and six years after that same biosimilar was approved by the FDA for commercialization in the United States.[33]

The legal interventions associated with anticompetitive behaviors of the type described above belong traditionally to the domain of antitrust law and policy. However, antitrust responses tend to lag in time, as exemplified by the case of Humira. While pay-for-delay can be configured as a core antitrust problem,[34] this does not mean that antitrust law and antitrust regulators are or should be the sole entities capable of addressing anticompetitive behaviors in the biopharmaceutical arena. This Article explores the possibility of a more immediate response to problems posed by pay-for-delay in the context of biologics than the one that antitrust regulators like the FTC, or the application of antitrust law, can provide.

---

large numbers of staggered patents while entering into agreements to restrict competition with generic or biosimilar manufacturers. *Infra*, Part III.

[29] *Infra*, Part III.

[30] See generally Heled, *Follow-On Biologics Are Set Up to Fail*, *supra* note 24. See also Carrier.

[31] See Carrier & Minniti, *Biologics: The New Antitrust Frontier*, supra note 12 (providing an overview of the application of antitrust law to the field of biologics).

[32] *Infra*, Part III.A.4.

[33] *Infra*, Part III.

[34] See Hovenkamp, *Antitrust and Innovation*, *infra* note 372 and accompanying text.

Because anticompetitive behaviors related to biopharmaceutical products arise in "shared regulatory space,"[35] it is worth asking if there are any other institutional players that are well placed to address pay-for-delay, without deviating from their mission and without interfering with unfolding, however slow, antitrust responses.

This Article answers that question by identifying the FDA as the natural locus for an intervention that would curb pay-for-delay and incentivize motivated biosimilar manufacturers to bring their products to market. Known as an institutional catalyst for the production of information and as a player in the administration of innovation policy,[36] the FDA acts also as the gatekeeper for biopharmaceutical products. In cases of pay-for-delay, a biopharmaceutical company elects to deliberately remain outside the market, going against the permissive gesture of the administrative agency approving a product at the request of that same company.

While it is a prerogative of the private company to refrain from commercializing its products, it is also a prerogative of the agency to withdraw approval if no manufacturing activity occurs within a reasonable period of time.[37] In fact, after examining the regulatory framework for license revocation, this Article argues that the FDA has not only the ability, but also the obligation to revoke biosimilar licenses in cases of pay-for-delay.

From a policy perspective, it is also desirable that the Agency do so. This solution eliminates some of the most troubling effects of the extended lag between anticompetitive settlements and antitrust litigation, while triaging the marketplace for biosimilar competition.[38] On the one hand, highly motivated players—in a field encompassing the most expensive drugs[39] in the world—will seek regulatory approval from the FDA if they intend to come to market. On the other, players unwilling to engage in patent litigation, or motivated primarily by the prospect of pay-for-delay, are now discouraged from (mis)using the regulatory pathway and will reallocate their resources and strategic priorities accordingly. In fact, resource reallocation has already started to happen in the case of biosimilars to Humira: with so many biosimilars approved by the FDA waiting to enter the market in 2023, companies have started shifting research and development (R&D) funds away from biosimilars to Humira and into other types of biosimilars.[40]

In addition to increasing costs for patients and health systems, the detrimental effects of pay-for-delay in the context of biologic-biosimilar competition are likely to extend into other areas. In 2018, as the number of agreements between the manufacturer of Humira and biosimilar companies grew progressively larger, the FDA Commissioner noted that competition-restricting agreements targeting biosimilars are likely to produce long-term effects and affect the incentives for the development of new biosimilars:

> the net result is a lopsided playing field that disincentives biosimilar developers from making the sizable investment in

[35] See Jody Freeman & Jim Rossi, *Agency Coordination in Shared Regulatory Space*, 125 HARV. L. REV. 1131, 1135 (2012) (noting that "[m]any areas of regulation and administration are characterized by fragmented and overlapping delegations of power to administrative agencies").

[36] *Infra*, Part IV.

[37] *Id.*

[38] *Infra*, Part IV.A.

[39] A field in which revenues are often measured in the billions. See *infra*, Part II.A.

[40] See Kelly Davio, *Momenta Drops Biosimilar Adalimumab from Pipeline*, CTR. BIOSIMILARS (Aug. 5, 2019) (describing the case of a company engaged in the development of a biosimilar to Humira that decided to halt ongoing R&D efforts and reallocate $100 million to the development of other biosimilars due to market saturation).

> bringing such products to market. I am concerned this will lead to reduced competition in the long-run and unsustainable costs for these treatments.[41]

But so far, neither the Agency nor commentators have considered a solution hiding in plain sight: license revocation, a counterpart to the FDA's power to grant licenses, monitor the production and commercialization of approved products and use information generated in connection with these products. Because manufacturers entering into pay-for-delay agreements fail to generate meaningful information about their approved biosimilars, this Article argues that inaction due to pay-for-delay, if unjustified under certain principles,[42] falls into the cases contemplated by law allowing the Agency to revoke market authorization.[43] Moreover, the regulatory language is not merely enabling, but rather mandatory: the FDA "shall" revoke licenses for biologic products whose manufacture it cannot monitor and properly evaluate.[44] The solution proposed in this Article is thus already embedded in the regulatory framework, needs no legislative intervention and does not constitute an additional burden to an administrative agency that is already resource-constrained.[45] Applying it, however, would have an immediate and important effect on the availability of less expensive versions of drugs that are critical to so many patients in the United States.

With several blockbuster biologics poised to start losing patent protections in years to come,[46] finding ways to disincentivize pay-for-delay in this field becomes especially relevant. In arguing in favor of an FDA intervention to curb pay-for-delay, this Article does not seek to minimize the role and centrality of the antitrust apparatus, but rather to uncover a localized fix that can help in diminishing the frequency and impact of a specific type of anticompetitive agreement. In doing so, this Article contributes to the literature on pay-for-delay and other anticompetitive behaviors in the biopharmaceutical arena, as well as to the larger ongoing debate surrounding the limitations of long-established antitrust responses to competition issues.[47] Additionally, it makes the case that the role of the FDA as a competition-distorting entity[48] capable of providing fixes to intersecting regulatory problems should be further explored within the FDA-as-locus-of-incentives literature. Secondary contributions include a descriptive account of waves of patent expirations in the pharmaceutical space;[49] a questioning and reframing of the licensing function of the FDA as

---

[41] U.S. FOOD & DRUG ADMIN., *Advancing Patient Care Through Competition—Speech by Scott Gottlieb* (Apr. 19, 2018).

[42] *Infra*, Part IV.C.2.

[43] *Infra*, Part IV.C.3.

[44] 21 C.F.R. § 601.5(b)(1) (2018).

[45] See e.g. Leslie Pray & Sally Robinson, *Addressing the FDA's Resource Challenges*, in CHALLENGES FOR THE FDA: THE FUTURE OF DRUG SAFETY, WORKSHOP, National Academies Press (2007), at 13 ("the FDA has been chronically under-funded in carrying out its responsibilities for ensuring the safety of drugs, medical devices, and the nation's food supply").

[46] *Infra*, Part I.B.2.

[47] See Kahn, *The New Brandeis Movement: America's Antimonopoly Debate*, *infra* note 373 and accompanying text.

[48] *Infra*, Part IV.B.

[49] *Infra*, Part I.

an administrative agency;[50] and analysis of regulatory language that reveals current frameworks to be more capacious than previously thought.[51]

The Article proceeds as follows. Part I surveys the phenomenon of temporally concentrated expirations of patent in the pharmaceutical space and explains the relationship between drug patents, prices and FDA-administered market exclusivities. Part II focuses on the emergence of biologics at the turn of the century as the most promising and expensive drugs available to patients, and the corresponding regulatory pathway created in 2010 for the approval of biosimilar versions of these drugs. Part III explores ongoing manifestations of pay-for-delay, presenting a case study on Humira. It then explores the limitations of current antitrust responses to the problems posed by pay-for-delay, highlighting the need for cumulative regulatory interventions. Part IV argues that the FDA is well positioned to perform one such intervention, and that the existing license revocation regime should be used when biosimilar manufacturers deliberately fail to bring their products to market after FDA approval. While the proposal does not require any legislative intervention, Part IV further sketches out supplemental iterations of the proposed solution, which would require different forms of implementation. A brief conclusion follows, emphasizing the welfare-enhancing and fairness goals served by the proposal.

I. PATENT LIFE AND DRUG PRICES

A. PHARMACEUTICAL PATENTS AND GENERIC COMPETITION

Pharmaceutical innovation has long been an intersectional area. It combines two seemingly straightforward propositions: the discovery and development of new (or better) human drugs is a desirable societal and public health goal; however, the arc of pharmaceutical research and development (R&D) is time-consuming, resource-intensive and fraught with scientific and technical challenges.

This worldview of the dynamics of pharmaceutical innovation—whether grounded on evidence or stemming from perceived imperatives—has become intertwined with discourses emphasizing the centrality of patents as drivers of pharmaceutical R&D and, ultimately, pharmaceutical innovation.[52] William Landes and Richard Posner have famously suggested that, under contemporary intellectual property paradigms, certain segments of the pharmaceutical industry offer "the strongest case for patents."[53] Similarly, the pharmaceutical industry has traditionally operated under a patent-centric ethos, both through its practices and by outwardly portraying patents as sine qua non catalysts of drug development.[54]

---

[50] *Infra*, Part IV.

[51] *Infra*, Part IV.C.3.

[52] See e.g. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEXAS L. REV. 503, 508 (2009) (describing the patent system as a means "to encourage socially valuable investments in R&D that firms would not otherwise make due to the profit-eroding effects of competition.") See also Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, at 78 (my copy) (detailing how prospect theory explains the role of patents in pharmaceutical R&D: "Prospect theory fits best in the pharmaceutical industry.").

[53] See e.g. WILLIAM W. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW, HARVARD UNIVERSITY PRESS (2003), at 316.

[54] Quote from Pharma. See also See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 346 (2007) (noting that "[t]he pharmaceutical industry (…) has sung the praises

Arguments surrounding the centrality of patents have progressively been challenged and refined in scholarship and in practice,[55] both generally and in the specific context of pharmaceuticals.[56] In some—albeit limited—areas of pharmaceutical R&D, scholars have found evidence that patents play a modest or virtually negligible role in driving innovation.[57] In a complementary vein, researchers have also shown that there are several other types of incentives that drive innovation—including pharmaceutical innovation—beyond the realm of patents,[58] such as prizes,[59] grants,[60] and insurance or reimbursement schemes.[61]

Even when considering the limitations of patent-focused narratives, the fact remains that the field of pharmaceuticals at large is characterized by innovation processes that are heavily reliant on patents.[62] Studies have estimated that a single pharmaceutical drug is on average covered

---

of the patent system as a means of promoting costly and risky investments in research and development"); Daniel J. Hemel & Lisa L. Ouellette, *Innovation Policy Pluralism*, 128 YALE L. J. 544, 544 (2019) (observing that the pharmaceutical industry is "a sector sometimes described as the poster child for the pure IP patent system").

[55] See e.g Heidi L. Williams, *How Do Patents Affect Research Investments?*, 9 ANN. REV. ECON., 441 (2017) (analyzing the effects of elements such as disclosure and prior technology on the alignment between the incentivizing functions of intellectual property and the social contributions generated by patenting activity); Laura Pedraza-Fariña, *The Social Origins of Innovation Failures*, 70 SMU L. REV. 377 (2017) (noting the failure of current patent models in supporting social network innovation) Joshua D. Sarnoff, *Government Choices in Innovation Funding (with Reference to Climate Change)*, 62 EMORY L.J. 1087, 1098 (2013) (underlying the coexistence of intellectual property rights and other types of incentives, including government funding). A notable exception to the centrality patents in pharmaceutical R&D has been documented by Amy Kapczynski in her study of the network performing R&D on flu vaccines. Amy Kapczynski, *Order Without Intellectual Property Law: The Flu Network as a Case Study in Open Science*, 102 CORNELL L. REV. 1539 (2017). See also Rachel E. Sachs, *The Uneasy Case for Patent Law*, *infra* note 57 and accompanying text.

[56] See Henry G. Grabowski et al., *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFF. 302 (2015); Hemel & Ouellette, *supra* note 54, at 593-601; Arti K. Rai et al., *Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery*, 8 YALE J. HEALTH POL'Y L. & ETHICS 1 (2008) (providing an early overview of collaborative modes of pharmaceutical R&D).

[57] See Kapczynski, *Order Without Intellectual Property Law*, *supra* note 55 and accompanying text; Rachel E. Sachs, *The Uneasy Case for Patent Law*, 117 Mich. L. Rev. 499 (2018) (arguing that the ongoing development of microbiome-based research would not be disrupted by the removal of patent incentives). See also Kevin Outterson, *The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law*, 67 U. PITT. L. REV. 67 (2005) (arguing that strong intellectual property rights undermine R&D focused on solving the problems posed by antibiotic resistance).

[58] See generally Nancy Gallini & Suzanne Scotchmer, *Intellectual Property: When Is It the Best Incentive System?*, 2 INNOVATION POL'Y & ECON. 51 (2002) (exploring incentives mechanisms beyond patents); Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525 (2001); Hemel & Ouellette, *Innovation Policy Pluralism*, *supra* note 54, at 551-558 (surveying the range of patent and non-patent incentives potentially available to innovators).

[59] See e.g. Michael Abramowicz, *Perfecting Patent Prizes*, 56 VAND. L. REV. 115 (2003) (proposing a prize system that would complement or even replace the patent system).

[60] See W. Nicholson Price II, *Grants*, 34 BERKELEY TECH. L.J. 1 (2019).

[61] See Rachel E. Sachs, *Prizing Insurance: Prescription Drug Insurance as Innovation Incentive*, 30 HARV. J.L. & TECH. 153 (2016); Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307 (2018).

[62] See Lisa L. Ouellette, *How Many Patents Does It Take to Make a Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 303 (2010) (citing empirical literature on the centrality of the role of patents in pharmaceutical R&D and labeling the pharmaceutical industry "the poster child for a strong patent system"). *Id.*, at 300).

by anywhere from 2.7 to 3.5 patents.[63] In the case of structurally more complex drugs like biologics,[64] that number can nowadays be significantly higher: for instance, Humira was at one point shielded from competition by more than 100 patents.[65]

In enabling innovators to exclude others from the marketplace,[66] the patent system gives rights holders the ability to price goods in monopoly-esque settings.[67] There is currently no other area in which this ability is as debated and contested as when pharmaceutical drugs are at stake.[68] Although patents alone cannot account for concerns surrounding the price of prescription drugs in the United States, they undoubtedly remain the primary tool through which market exclusion occurs.[69]

Even in a patent-dense environment such as the pharmaceutical innovation arena, there are in-built systemic features designed to counterbalance the anti-competitive effects of exclusivity.[70] One of the most salient is the temporary duration of patents, limited to 20 years.[71] In the case of pharmaceutical drugs, the actual length of exclusivity has been shown to be shorter than the legal term, as a combination of early patenting practices and lengthy regulatory approval eat into the lifetime of most patents.[72]

Once the term expires, competitors are in theory able to enter the market, thereby driving down the cost of goods. In the case of pharmaceutical drugs, market entrance may be further delayed if there are non-patent exclusivities at play.[73] A set of statutory exclusivities prevents the approval of generics for certain periods of time, even if patent protection has ended. For instance, in cases where the original drug manufacturer has obtained FDA approval for a new chemical entity, the Agency is barred from approving generic applications for a period of five years,

---

[63] See Scott Hemphill & Bhaven Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 338 (2012) (putting the number of average patents covering a single pharmaceutical drug at 2.7); Ouellette, *How Many Patents Does It Take to Make a Drug?*, *supra* note 62, at 300 (referencing studies using different metrics to reach an average of 3.5).

[64] *Infra*, Part II.A.

[65] Richard Gonzalez, CEO of AbbVie, the manufacturer of Humira, has stated that the company has been awarded 136 Humira-related patents. See *Drug Hearing Produces Few Fireworks as Slog Toward Fixes Begins*, BLOOMBERG LAW, available at https://news.bloomberglaw.com/pharma-and-life-sciences/drug-hearing-produces-few-fireworks-as-slog-toward-fixes-begins (last accessed Jan. 9, 2020). See also *infra*, Part III.A.

[66] Cfr. 35 U.S.C. § 271(a).

[67] But see e.g. Benjamin N. Roin, *Intellectual Property Versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999, (2014) (arguing that the existence of intellectual property rights cannot be equated with "uniform monopoly pricing and monopoly profits").

[68] See e.g. Robert Pearl, *Why Patent Protection in The Drug Industry Is Out Of Control*, FORBES (Jan. 19, 2017).

[69] Other tools include additional market exclusivities granted by the U.S. Food and Drug Administration. See generally Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. TECH. L. REV. 419 (2012).

[70] The U.S. Constitution takes an inherently limiting approach to patent rights, which are granted "for limited times" and with the purpose "[t]o promote the Progress of . . . useful Arts" U.S. CONST. art. I, § 8, cl. 8.

[71] 35 U.S.C. § 154 (a)(2).

[72] See e.g. Erika F. Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39 (2018) (citing several studies exploring the length and underlying justifications for the shorter de facto period of exclusivity).

[73] See Heled, *supra* note 69. See also Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L. REV. 299 (2015). See also *infra*, Part I.B (describing the case of the first generic drug competing with Prozac, for which there was a six-month period of statutory exclusivity).

irrespective of patent expiration.[74] Similarly, when a drug manufacturer is granted approval for a new indication for previously approved drugs, a three-year exclusivity period applies.[75] These exclusivities were introduced in 1984 by the Hatch-Waxman Act,[76] with the purpose of providing original drug manufacturers with additional incentives to engage in R&D.[77] In return, Hatch-Waxman created a streamlined pathway for the approval of generics, a process that until then required manufacturers to conduct their own clinical trials, thereby rendering regulatory review too resource-intensive and expensive for would-be generic drug sponsors.[78]

Even competition among generic drugs—which are by definition unpatentable versions of previously approved drugs—may be temporarily postponed due to FDA exclusivities. The first generic manufacturer to file an application for FDA approval that successfully challenges a patent on an approved drug is entitled to a 180-day period of exclusivity, during which other generic manufacturers are unable to enter the market.[79]

This statutory exclusivity regime applies to most of the drugs currently on the market: small-molecule drugs, also known as conventional drugs, which are the product of chemical synthesis. Examples include aspirin, drugs used in the treatment of high cholesterol levels and drugs used in the treatment of hepatitis C. In addition to being small, conventional drugs are structurally simple, stable, easy to characterize, manufacture and to replicate. Large-molecule drugs, known as biologics, possess the opposite characteristics and are subject to a different regulatory regime, addressed in Part II.

Released from the requirement of conducting expensive clinical trials since the mid-1980s,[80] generic manufacturers have been able to cheaply produce their versions of brand-name conventional drugs. In 2018 alone, the FDA approved or tentatively approved 1,021 generic applications.[81] The Agency relies on studies estimating that generic drugs cost on average 85%

---

[74] 21 U.S.C. § 355(c)(3)(E)(ii).

[75] 21 U.S.C. §§ 355(c)(3)(E)(iii)–(iv).

[76] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98- 417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, and 42 U.S.C.). The first statutory exclusivity dates back to 1983, when Congress enacted the Orphan Drug Act, which established a 7-year exclusivity for drugs targeting diseases that affect small patient populations (currently defined as 200,000 or fewer patients in the United States). Pub. Law No. 97-414, 96 Stat. 2049 (1983) (codified as amended in various sections of 21, 26, 35, & 42 U.S.C.). See also U.S. FOOD & DRUG ADMIN., DEVELOPING PRODUCTS FOR RARE DISEASES & CONDITIONS, https://www.fda.gov/industry/developing-products-rare-diseases-conditions (last accessed Jan. 9, 2020).

[77] See Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 727 (framing the Hatch-Waxman Act as "a complex legislative compromise between the interests of research pharmaceutical firms and generic competitors").

[78] *Id.*, *ib.*

[79] 21 U.S.C. § 355(j)(5)(B)(iv) (laying out the 180-regulatory exclusivity); 21 U.S.C. § 355(j)(5)(B)(iv)(II) (laying out the framework for the corresponding patent challenge). See also Heled, *Patents vs. Statutory Exclusivities*, *supra* note 69, at 428-429 (explaining the generic 180-day exclusivity as an incentives mechanism).

[80] 21 U.S.C. § 355(j)(2) (listing the information required for an abbreviated new drug application (ANDA), the type of application required for generic manufacturers seeking market entrance). Since the law no longer requires a demonstration of safety and effectiveness, generic manufacturers are able to rely on data submitted by original drug sponsors instead of running their own clinical trials.

[81] U.S. FOOD & DRUG ADMIN., 2018 OFFICE OF GENERIC DRUGS ANNUAL REPORT, https://www.fda.gov/drugs/2018-office-generic-drugs-annual-report (last accessed Jan. 9, 2020).

less than brand-name drugs[82] and translate into significant savings to the United States healthcare system. Sources used by the FDA have calculated that, between 2007 and 2016, those savings have amounted to USD 1.67 trillion.[83]

While the introduction of generics has many positive social and economic dimensions, from the perspective of brand-name pharmaceutical companies it marks the downturn in the lifetime of a drug once sheltered from competition. The Article now turns to that point in time, paying particular attention to the first waves of patent expirations the pharmaceutical industry.

B. First Waves of Patent Expiration: Conventional Drugs

As seen above, even though they are relatively simple when compared to large-molecule drugs, conventional drugs are covered by multiple patents.[84] When the main patent, or several of the most relevant patents,[85] covering a pharmaceutical drug approach their term, that drug is said to be facing a patent cliff.[86] The expression has become closely associated with points in time in which multiple drugs—and especially blockbuster drugs—simultaneously approach the end of patent life.[87] Over the past decade, there have been three important waves of pharmaceutical patent expirations, which this Article addresses in the following subsections. Some commentators see the ongoing wave—affecting biologics—as the tail end of the second wave.[88] For reasons developed below, among which the fact that we are currently dealing with the first wave of patent expirations involving biologic products, this Articles argues that the ongoing wave is best understood as a separate wave.

1. The First Waves of Patent Expiration

The first major wave of patent expirations involving pharmaceuticals dates back to 2001, when the generic version of Prozac entered the market.[89] Prozac is a small-molecule drug used in

---

[82] U.S. Food & Drug Admin., Generic Drug Facts, https://www.fda.gov/drugs/generic-drugs/generic-drug-facts (last accessed Jan. 9, 2020) (citing information provided by IMS Health Institute).

[83] *Id.*, *ib.*

[84] Ouellette, *How Many Patents Does It Take to Make a Drug?*, *supra* note 62, at 300.

[85] For instance, the patent covering the composition of a drug.

[86] See Charlotte Harrison, *The Patent Cliff Steepens*, 10 Nature Reviews Drug Discovery 12 (2011); Charlotte Harrison, *Dangling from the Patent Cliff*, 12 Nature Reviews Drug Discovery 14 (2013);

[87] See e.g. Jack DeRuiter & Pamela L. Holston, *Drug Patent Expirations and the "Patent Cliff,"* 37 U.S. Pharm. 12 (Jun. 20, 2012) ().

[88] See e.g. Ed Silverman, *Strap on Your Parachutes, Pharma Faces a Mini Patent Cliff*, Stat (Apr. 26, 2017). For reasons developed in the following sections, among which the fact that currently we are dealing with the first wave of patent expirations involving biologic products, this Articles argues that the ongoing wave is best understood as a separate phenomenon.

[89] *See* Benjamin G. Druss et al., *Listening to Generic Prozac: Winners, Losers, and Sideliners*, 23 Health Affairs, 210, 210 (2014) (noting that "[t]he release of generic fluoxetine [an antidepressant agent for which Prozac is one of the brand names] in August 2001 marked the beginning of the largest patent expiration cycle in the history of the pharmaceutical industry").

the treatment of several conditions, including depression.[90] First approved by the FDA in 1987,[91] it has been described as a "breakthrough drug."[92] Until then, there were other types of antidepressant drugs available to patients, but they operated differently.[93] Studies indicated that Prozac was comparatively superior to these older drugs, causing fewer and less severe side effects.[94] It was also widely marketed as a "wonder drug"[95] and quickly became a best-seller, a status it maintained until the turn of the century.[96]

The active ingredient in Prozac, fluoxetine, was first identified as a potential antidepressant in the 1970s by scientists working at Eli Lilly, an Indiana-based pharmaceutical company.[97] Starting in 1974, Eli Lilly applied for several fluoxetine-related patents, which the U.S. Patent and Trademark Office (PTO) granted through the mid-1980s.[98] Following FDA approval, Prozac entered the United States market in January 1988.[99]

While on patent, Prozac sales reached as high as $2.8 billion in a single year.[100] It became the largest-grossing drug in its category, and the fifth most prescribed drug in the United States.[101] The last standing patent covering Prozac expired in August 2001,[102] clearing the field for

---

[90] U.S. FOOD & DRUG ADMIN., PROZAC LABEL, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018936s076lbl.pdf (last accessed Jan. 9, 2020).

[91] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018936s091lbl.pdf (last accessed Jan. 9, 2020).

[92] David T. Wong et al., *The Discovery of Fluoxetine Hydrochloride (Prozac)*, 4 NATURE REV. DRUG DISCOVERY 764 (2005) (describing the active component in Prozac as "widely acknowledged as a breakthrough drug for depression"). See also PROZAC: REVOLUTION IN A CAPSULE, N.Y. TIMES (1994), https://www.nytimes.com/video/us/100000003127845/revolution-in-a-capsule.html?playlistId=100000002148738 (last accessed Jan. 9, 2020).

[93] See generally Todd M. Hillhouse & Joseph H. Porter, *A Brief History of the Development of Antidepressant Drugs: From Monoamines to Glutamate*, 23 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 1 (2015).

[94] Barry H. Guze & Michael J. Gitlin, *New Antidepressants and the Treatment of Depression*, 38 J. FAM. PRAC. 49 (1994) (noting that Prozac was as effective as pre-existing drugs, but generally considered safer). But see Natalie Anger, *Eli Lilly Facing Million-Dollar Suits on Its Antidepressant Drug Prozac*, N.Y. TIMES (Aug. 16, 1990), https://www.nytimes.com/1990/08/16/us/health-eli-lilly-facing-million-dollar-suits-on-its-antidepressant-drug-prozac.html (last accessed Jan. 9, 2020) (describing litigation against the manufacturer of Prozac for failure to properly warn consumers about the side effects of the drug).

[95] Mary O'Hara & Pamela Duncan, *Why 'Big Pharma' Stopped Searching for the Next Prozac* (Jan. 27, 2016), https://www.theguardian.com/society/2016/jan/27/prozac-next-psychiatric-wonder-drug-research-medicine-mental-illness (last accessed Jan. 9, 2020) (describing how Prozac was marketed as a "wonder drug").

[96] See CLARK LAWLOR, FROM MELANCHOLIA TO PROZAC: A HISTORY OF DEPRESSION, OXFORD UNIVERSITY PRESS (2012), at 176.

[97] Cody Wenthur, *Classics in Chemical Neuroscience: Fluoxetine (Prozac)*, 5 AM. CHEM. SOC'Y CHEM. NEUROSCI. 14 (2014) (noting that sales of Prozac peaked in 1998).

[98] U.S. Patent No. 4,018,895; U.S. Patent No. 4,314,081; U.S. Patent No. 4,590,213; U.S. Patent No. 4,626,549.

[99] U.S. FOOD & DRUG ADMIN., PROZAC LABEL, supra note 90.

[100] See Wenthur, *supra* note 97. See also Druss, *supra* note 89, at 210 (reporting that Prozac averaged USD 2.7 billion in annual sales while on patent, according to an IMS Health study on the ten best-selling drugs in the U.S. market by sales volume).

[101] Druss, *ib.*

[102] Eli Lilly sought to prevent Prozac competitors from entering the market until 2003, but the Federal Circuit held that the latest-expiring patent covering Prozac was invalid due to double-patenting. *Eli Lilly & Co. v. Barr Labs, Inc.*, 222 F.3d 973, 55 U.S.P.Q.2d 1609 (Fed. Cir. 2000) (holding that the '549 patent was invalid on grounds of obviousness with reference to the '895 patent); *Eli Lilly & Co. v. Barr Labs, Inc.*, 251 F.3d 955, 58 U.S.P.Q.2d 1865

manufacturers of generic fluoxetine to compete with Eli Lilly. Twenty weeks after the generic version of Prozac entered the market, generic fluoxetine accounted for 69.6% of all fluoxetine prescriptions in the United States.[103] Nearly three quarters of patients (73.8%) previously taking Prozac switched to the generic.[104] A majority of new users of fluoxetine (65.8%) were started on the generic instead of Prozac.[105]

The generic was initially priced at $1.91 per unit, 12% less than Prozac's price per unit.[106] The price of the generic did not change for the first six months, which corresponded to the period of statutory exclusivity awarded to Barr Laboratories, the first manufacturer of generic fluoxetine.[107] As exclusivity came to an end and other manufacturers were able to enter the market and compete with Barr Laboratories, the price of generic fluoxetine decreased significantly and quickly: during the year that followed the end of statutory exclusivity, it went down to $0.32 per unit, or a factor of six.[108] Generic competition had the opposite effect on the price of Prozac: during the same period of time, the price per unit increased from $2.25 to $2.40.[109]

Even though Prozac was priced higher than before, generic substitution sharply curtailed its revenue stream. By 2005, Prozac was generating $453 million in sales, down from the $2.7 billion it was averaging while on patent.[110] Referencing the moment of patent expiration in 2001, a commentator observed that Prozac's manufacturer "lost US $35 million of its market value in a single day."[111]

In the years after Prozac began facing generic competition, other drugs used as antidepressants also went off-patent.[112] Zoloft, a small-molecule drug manufactured by Pfizer and marketed in the United States since 1991, was (and is) used to treat a range of conditions that overlap with those targeted by Prozac.[113] Although both drugs belong to the same class,[114] Zoloft's

---

(Fed. Cir. 2001) (vacating the 2000 decision, but still holding the '549 patent invalid on grounds of obviousness, now with reference to the '213 patent).

[103] Druss, *supra* note 89, at 211 (noting also that "the proportion of fluoxetine users in the population did not change after the introduction of the generic").

[104] *Id., ib.*

[105] *Id., ib.* The Druss study also showed that the substitution effect was limited to Prozac, noting that only 0.9% of patients treated with antidepressant drugs other than Prozac switched to generic fluoxetine ("There was almost no evidence of switching to generic fluoxetine among patients treated with medications other than Prozac"). *Id.*, at 213.

[106] *Id.*, at 213.

[107] *Id., ib.* See also *infra*, Part I.A.

[108] *Id.*, at 213-214.

[109] *Id., ib.*

[110] Aaron Smith, *Who Stands To Gain When Zoloft Goes Generic?*, CNN MONEY (Apr. 4, 2006), https://money.cnn.com/2006/04/04/news/companies/antidepressants/ (last accessed Jan. 9, 2020). See also *supra* note 100 and accompanying text.

[111] Wenthur, *supra* note 97.

[112] Druss, *supra* note 89, at 214.

[113] U.S. FOOD & DRUG ADMIN., ZOLOFT, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019839s070,020990s032lbl.pdf (last accessed Jan. 9, 2020).

[114] Collectively, the drugs referenced in this section belong to the class of selective serotonin reuptake inhibitors, commonly known as SSRIs. See U.S. FOOD & DRUG ADMIN., SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) INFORMATION, https://www.fda.gov/drugs/information-drug-class/selective-serotonin-reuptake-inhibitors-ssris-information (last accessed Jan. 9, 2020).

active ingredient is different from Prozac's.[115] Pfizer held two patents on Zoloft.[116] While on patent, Zoloft generated on average over $2 billion in revenue per year.[117] In 2005, the last full year before the patent on Zoloft's composition expired, that number had surpassed the $3 billion barrier.[118] As Zoloft lost patent protection[119] in June 2006, the first generic version of the drug entered the United States market.[120] Pfizer's revenue was immediately projected to go down to $470 million.[121]

While the pronounced decline in the sales of Prozac and Zoloft illustrates how generic competition leads to immediate market erosion, patent expiration does not normally extinguish the demand for brand-name drugs. For instance, three and a half years after losing patent protection, Zoloft was earning Pfizer $516 million globally.[122] In 2016, that number had decreased to $304 million.[123] According to the latest available data, pertaining to 2018, Zoloft generated $298 million.[124] Prozac sales, as seen above, saw a similar downwards trajectory.[125]

Globally, in the wake of the 2001 patent expiration wave, R&D on psychiatric drugs diminished considerably, with some studies estimating that decrease at around 70%.[126] At the same time, the use of antidepressants went up.[127] This is not to say that patent expiration and loss of regulatory exclusivities are the sole causes of decline in R&D in the conventional drug space. After a period of scientific breakthroughs and commercial growth, it has also become more difficult to develop new small-molecule drugs.[128]

---

[115] Sertraline hydrochloride.

[116] U.S. Patent No. 4,536,518 (covering the drug's composition); U.S. Patent No. 5,248,699 (covering another form of the drug, as well as a method of preparation).

[117] *Teva Pharmaceuticals USA v. Pfizer*, 395 F.3d 1324 (Fed. Cir. 2005).

[118] Smith, *supra* note 110 (putting the number at USD 3.3 billion).

[119] For the '518 patent, covering the drug's composition; see *supra* note 116. See also *Teva Pharmaceuticals USA v. Pfizer*, *supra* note 117 (describing the patent challenges brought by Teva prior to introduction of its generic version of Zoloft on the market).

[120] Smith, *supra* note 110.

[121] *Id.*

[122] PFIZER, FULL-YEAR 2009 RESULTS, https://www.pfizer.com/news/press-release/press-release-detail/pfizer_reports_fourth_quarter_and_full_year_2009_results_provides_2010_financial_guidance_and_2012_financial_targets (last accessed Jan. 9, 2020).

[123] PFIZER, FULL-YEAR 2016 RESULTS, https://s21.q4cdn.com/317678438/files/doc_news/2016/Q4_2016_PFE_Earnings_Press_Release_dwerfks.pdf (last accessed Jan. 9, 2020).

[124] PFIZER, FULL-YEAR 2018 RESULTS, https://s21.q4cdn.com/317678438/files/doc_financials/Quarterly/2018/q4/Q4-2018-PFE-Earnings-Release.pdf (last accessed Jan. 9, 2020).

[125] This category includes Prozac, Prozac Weekly and Eli Lilly's own generic version of the drug used to treat premenstrual dysphoric disorder, Sarafem. See ELI LILLY, ANSWERS FOR SHAREHOLDERS 2004, https://investor.lilly.com/static-files/67d703e8-99e6-49e6-836d-4c39686df4c2 (last accessed Jan. 9, 2020), at 9.

[126] O'Hara & Duncan, *supra* note 95.

[127] *Id., ib.*

[128] Freudenheim & Petersen, *supra* note **Error! Bookmark not defined.**.

The second wave, which began around 2011[129] and affected the then-largest grossing drug in the world, Lipitor,[130] also needs to be understood against a broader context. Several studies published in 2012 reported that, for the first time in over two decades, spending on prescription drugs in the United States had declined[131] as a result of an economic downturn.[132] A study by IMS Health calculated a decrease of 1% in nominal drug spending in the United States,[133] while another, by Express Scripts, put that number at 1.5%.[134] According to the latter study, the majority of drugs contributing to the 1.5% drop were "traditional prescription drugs" treating "common diseases" like high blood pressure.[135] For drugs targeting "more complex diseases," including oncology and autoimmune conditions, the same study reported an actual increase of 18.4%.[136] Many of these complex medical conditions are now treated by large-molecule drugs, which until much more recently had never faced exposure to follow-on competitors.

2. The New Wave of Patent Expiration

Between 2016 and the mid-2020s, a significant number of commercially successful drugs have lost or are expected to lose patent protection. Among these, there are several small-molecule drugs, including Truvada, a drug used in the treatment and prevention of acquired immunodeficiency syndrome (AIDS),[137] whose key patent on composition expired in 2017;[138] Lyrica, an anti-epileptic drug also used in the treatment of nerve pain (fibromyalgia),[139] which lost

[129] See Harrison, *The Patent Cliff Steepens*, *supra* note 86.

[130] Lipitor is a small-molecule drug used in the treatment of high cholesterol.

[131] A study by the IMS Health calculated the total of nominal drug spending in the U.S. in 2012 to have reached USD 325.8 billion. See Tracy Staton, *Behold the Patent Cliff: U.S. Drug Market Shrinks for First Time*, FIERCEPHARMA (May 9, 2013), https://www.fiercepharma.com/regulatory/behold-patent-cliff-u-s-drug-market-shrinks-for-first-time (last accessed Jan. 9, 2020) (citing the IMS study, and further reporting that per capita spending was calculated to have dropped by 3.5%).

[132] *Behold the Patent Cliff: U.S. Drug Market Shrinks for First Time*, FIERCEPHARMA (May 9, 2013), https://www.fiercepharma.com/regulatory/behold-patent-cliff-u-s-drug-market-shrinks-for-first-time (l last accessed Jan. 9, 2020) (further reporting that per capita spending was calculated to have dropped by 3.5%).

[133] *Id., ib.*

[134] EXPRESS SCRIPTS, 2012 DRUG TREND REPORT (Mar. 5, 2013), https://lab.express-scripts.com/lab/insights/industry-updates/2012-drug-trend-report (last accessed Jan. 9, 2020). See also generally EXPRESS SCRIPTS, 2012 EXPRESS SCRIPTS DRUG TREND REPORT (on file with author).

[135] EXPRESS SCRIPTS, 2012 DRUG TREND REPORT, *supra* note 134.

[136] *Id.*

[137] Trudy Ring, *FDA Approves Generic Version of Truvada*, HIV PLUS (Jun. 20, 2018) (also noting Truvada cost $1,500 per month while on-patent). Also nod to patent government episode.

[138] The patent covering tenofovir disoproxil fumarate expired in July 2017. Another patent on Truvada's composition, covering emtricitabine, was the source of much… https://www.pharmacytimes.com/resource-centers/hiv/truvada-commercial-during-rent-live-sparks-dialogue-about-prep-accessibility.

[139] U.S. FOOD & DRUG ADMIN., MEDICATION GUIDE: LYRICA, https://www.fda.gov/media/76602/download.

patent protection in 2019;[140] and Tecfidera, used in the treatment of relapsing multiple sclerosis,[141] which is losing key patents in 2019 and currently faces a patent challenge that could allow for generic competition as early as 2020.[142]

Before losing patent protection, Truvada generated up to $2.6 billion per year in sales in the United States.[143] Lyrica averaged sales in excess of $3 billion in the United States in the years prior to patent expiration,[144] while Tecfidera averaged $4 billion.[145] As in previous instances of patent expirations, as manufacturers of generics are allowed to enter the market, revenues associated with these drugs are projected to decline.[146]

Given the proximity between the tail end of the 2011 wave and the ongoing loss of patent and exclusivity protection affecting several blockbuster drugs, some commentators see a continuity between the second wave and the ongoing one.[147] The wave that began in 2016, however, is significantly different from previous ones, as it includes for the first time the larger, more complex drugs known as biologics.[148] This Article thus treats the 2016 wave separately, not only materially, but also because it takes the view that the legal and policy problems posed by competition involving biologic drugs should be addressed in significantly different ways from the ones adopted in connection with the 2001 and 2011 waves.[149] The characteristics of biologics and the challenges related to biologic competition are addressed, respectively, in Parts II and III.

Among the biologics losing patent protection during the current wave is the largest-grossing drug (of any kind) in the world, Humira, which is the subject of a case study in Part III. Several other blockbuster biologics will face the loss of total or partial patent protection during the ongoing wave. These include Rituxan, used in the treatment of some cancers and rheumatoid arthritis, among other indications,[150] whose patent estate began expiring in 2018;[151] Herceptin,

---

[140] Eric Sagonowsky, *Pfizer Wins Blockbuster Lyrica Patent Extension to Safeguard Sales till June*, FIERCEPHARMA (Nov. 28, 2018) (describing how Lyrica enjoyed patent protection until the end of 2018, followed by regulatory exclusivity through the end of June 2019).

[141] U.S. FOOD & DRUG ADMIN., APPROVAL PACKAGE (TECFIDERA), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204063Orig1s010.pdf.

[142] Eric Sagonowsky, *Biogen Faces Multibillion-Dollar Tecfidera Loss if Mylan Wins Latest Patent Threat*, FIERCEPHARMA (Feb. 7, 2019).

[143] *Id.*, *Gilead's $3B Truvada Will Face Generics a Year Early. Can Descovy Still Win Over Its Patients?*, FIERCEPHARMA (May 9, 2019) (additionally reporting worldwide sales of Truvada reaching $3 billion in 2018).

[144] Kyle Blankenship, *Truvada*, FIERCEPHARMA (Jun. 17, 2019) (citing $3.59 billion for 2018).

[145] *Biogen Reports Record Revenues for Both the Full Year and Fourth Quarter of 2017, $12.3 Billion and $3.3 Billion, Respectively*, BUSINESS WIRE (Jan. 25, 2018). See also Jonathan Gardner, *After Alzheimer's Collapse, Biogen Must Win Tecfidera Patent Challenge*, EVALUATE (Mar. 25, 2019).

[146] See e.g. Phil Taylor, *As Lyrica Patent Expiry Looms, Pfizer Buys Array for $11.4bn*, PHARMAPHORUM (Jun. 17, 2019) (describing the expected impact of generic competition on Lyrica sales).

[147] Silverman, *Strap on Your Parachutes, supra* note 88 (quoting an industry analyst stating that "[i]t may be incorrect to claim that the [2011]'patent cliff' has passed").

[148] *Id., ib.* (acknowledging that biologic drugs are facing a so-called "patent cliff" for the first time).

[149] See *infra*, Parts IV.B and V (arguing that reliance on antitrust tools should be complemented by a stricter approach to the FDA's power to grant licenses covering pharmaceutical drugs).

[150] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION (RITUXAN), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf.

[151] *Roche's Blockbuster Oncology Drugs Losing Steam as They Approach Patent Expiry*, Forbes (Oct. 12, 2017).

widely used in the treatment of breast cancer,[152] which lost patent protection in the U.S. in 2019;[153] and Avastin, an oncology drug that is also used in the treatment of eye disease,[154] which also lost patent protection in the United States in 2019 and is set to lose protection in Europe in 2022.[155]

While on patent, these three biologics were among the best-selling drugs domestically and abroad. During the last year of full patent protection, Herceptin and Avastin generated $2.5 billion and $3 billion, respectively, in the United States market.[156] Rituxan, exposed earlier to competition, had sales declining from $7.32 billion in 2015[157] to $4.92 billion in 2018,[158] and is predicted to endure further erosion as competitors enter the market.[159]

II. BIOLOGICS AND PATENT TERM EXPIRATION

A. BIOLOGICS: "THE MOST PROMISING DRUGS"

Biologics are large-molecule drugs made of living materials.[160] Their structure is so complex that they have been contrasted with conventional drugs in the following way: "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."[161]

Unlike small-molecule drugs, which are chemically synthesized, biologics are also difficult to characterize and sensitive to manufacturing changes.[162] In addition to rendering them costly to develop, this makes biologics very hard to replicate in sharp contrast with conventional drugs, which are easily reverse-engineered.[163]

At the same time, biologics are widely considered among the "most promising"[164] drugs available to patients today.[165] They are currently used to treat a wide array of diseases, from several

---

[152] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION (HERCEPTIN), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf.

[153] *FDA Approves Herceptin Biosimilar as U.S. Patent Expires*, PHARMAPHORUM (Jun. 14, 2019).

[154] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION (AVASTIN), https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s301lbl.pdf.

[155] *FDA Approves Bevacizumab Biosimilar Mvasi*, GENERICS AND BIOSIMILARS INITIATIVE (2017).

[156] Amy Brown, *Roche Dominates 2019's Big Patent Expiries*, EVALUATE (Jan 21., 2019) (reporting revenue from 2018). As of late 2018, Herceptin and Avastin had generated $43.1 billion and $49.4 billion, respectively, in lifetime sales. *Id.*

[157] Michael Gibney, *Rituxan*, FIERCEPHARMA (2016).

[158] Eric Saganowski, *Rituxan*, FIERCEPHARMA (Feb. 26, 2019).

[159] *Id.*

[160] See *supra* note 1 and accompanying text.

[161] Price & Rai, *Manufacturing Barriers*, *supra* note 9, at 1026.

[162] U.S. FOOD & DRUG ADMIN., *What Are "Biologics"*, *supra* note 11, at 1026.

[163] See Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439 (2007); see also DAN L. BURK & MARK LEMLEY, THE PATENT CRISIS, at 39.

[164] Price II & Arti K. Rai, *Manufacturing Barriers*, *supra* note 9, at 1026.

[165] U.S. FEDERAL TRADE COMM'N, EMERGING HEALTHCARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (2009) (report available at https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-

types of cancer to common inflammatory diseases including lupus, rheumatoid arthritis and Crohn's. They are also among the most expensive drugs in the market. Herceptin, one of the biologics that lost patent protection in 2019,[166] cost $54,000 per year in 2012[167] and as much as $70,000 in 2016.[168] The anti-rheumatoid Humira, which has been the world's best-selling drug for several years, costs up to $50,000 a year in the United States,[169] even though several critical patents on the drug have expired.[170] Over the last few years, very promising gene therapies approved by the FDA were (at least initially) priced in the high six digits.[171] And very recently, Zolgensma,[172] a gene therapy targeting a rare form of muscular atrophy, broke the $2 million barrier.[173]

While biologic products have been on the market since the mid-1980s,[174] when the FDA approved the first therapeutic monoclonal antibody,[175] the boom in the commercialization of biologics–especially the more complex ones—did not take place until the turn of the century.[176] Rituxan, Herceptin and Avastin, three of the leading oncology drugs losing patent protection, were approved in 1997, 1998 and 2004, respectively. These are among the increasing number of biologics now approaching the end of their patent life or exclusivity period, or both.

Throughout the 2000s, biologics entering the United States market faced virtually no competition. As described in Part I, a regulatory pathway for the approval of generic versions of

---

follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf); Bahija Jallal, *Realizing the Promise of Biologics*, HARV. HEALTH POL'Y REV. (Apr. 9, 2017).

[166] *Supra*, Part I.

[167] See Tracy Staton, *FDA Approves Roche's Pricey New Herceptin Partner, Perjeta*, FIERCEPHARMA (Jun 11, 2012) (citing a monthly cost of $4,500).

[168] See Ed Silverman, *Genentech Accused Again of Cheating Health Care Providers*, STAT (Mar. 20, 2016).

[169] See Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions*, NY TIMES (Jul. 15, 2016).

[170] *Infra*, Part III.A.

[171] See Emily Mulin, *Tracking the Cost of Gene Therapy*, MIT TECH. REV. (Oct. 24, 2017) (listing price tags between $373,000 and $1 million the gene therapies commercialized under the brand names Kymriah, Strimvelis, Luxturna and Glybera).

[172] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION (ZOLGENSMA), https://www.fda.gov/media/126109/download.

[173] See e.g Rob Stein, *At $2.1 Million, New Gene Therapy Is The Most Expensive Drug Ever*, NPR (May 24, 2019); John Miller & Carolyn Humer, *Novartis $2 Million Gene Therapy For Rare Disorder Is World's Most Expensive Drug*, REUTERS (May 24, 2019). See also Bill Cassidy, *How Will We Pay For The Coming Generation of Potentially Curative Gene Therapies?*, STAT , (Jun. 12, 2019) (outlining both newly adopted and proposed payment solutions to address the cost of expensive drugs, and which could be potentially applicable to gene therapies); Mark R. Trusheim et al., *Alternative State-Level Financing for Hepatitis C Treatment—The "Netflix Model,"* 320 J. AM. MED ASS'N 1977 (Nov. 18, 2018) (providing background on Cassidy's proposal).

[174] See Mukherjee, *Protect at All Costs*, *supra* note **Error! Bookmark not defined.** (framing the FDA approval of the first immunosuppressant as the de facto moment in which biologics entered the United States market).

[175] *Id., ib*. See also Dawn M. Ecker et al., *The Therapeutic Monoclonal Antibody Market*, 7 MABS 9, 9 (2015). Prior to 1986, insulin and several therapeutic proteins had also entered the United States market through the FDA's NDA (new drug application) pathway—which technically applies to small-molecule drugs—and not the BLA (biologic license application) pathway. See Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 684-685 (2010).

[176] U.S. FOOD & DRUG ADMIN., BIOLOGICAL APPROVALS BY YEAR (databases available at https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/default.htm).

small-molecule drugs was created by the Hatch-Waxman Act in 1984.[177] As a result, the generic industry soared.[178] Hatch-Waxman, however, provided no similar avenue for large-molecule drugs. This scenario changed in 2010, with the enactment of the Biologics Price Competition and Innovation Act,[179] a component of the Affordable Care Act package.[180] The Act established an abbreviated pathway for the approval of drugs that are biosimilar or interchangeable with an already approved biologic. These follow-on biologics cannot be properly characterized as generics, as it is technically impossible to create a replica of a biologic drug. But follow-on biologics were expected to offer a clinically equivalent alternative to originator biologics, as well as a relatively more affordable one.

From a regulatory perspective, one of the main contrasts between small-molecule drugs and biologics is that the period of FDA-administered exclusivity regime is significantly different. Conventional drugs benefit from a period of five years of protection over clinical trial data, independent of the status of patent protection.[181] The period of market exclusivity often expires before patents covering small-molecule drugs do.[182] Biologics, on the other hand, benefit from a much longer exclusivity period, currently set at 12 years.[183]

B. FOLLOW-ON BIOLOGICS

The result of protracted negotiations,[184] the Biologics Price Competition and Innovation Act (BPCIA) was enacted in 2010, a few years before the beginning the first wave of patent term expiration for biologic drugs took place, and around the time the second wave of patent term expiration for conventional drugs began unfolding.

Like Hatch-Waxman, the BPCIA created an expedited review and approval process for second-comers wishing to compete with a drug previously approved by the FDA.[185] Unlike conventional drugs covered by Hatch-Waxman, biologic drugs cannot be replicated to create generic versions. As a result, the BPCIA establishes an abbreviated pathway for the licensure of

---

[177] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98- 417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, and 42 U.S.C.).

[178] See Aaron S. Kesselheim and Jonathan J. Darrow, *Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era?*, 15 Yale J. Health Pol'y L. & Ethics 295, 307-312 (2015).

[179] Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119, 804 (2010) (codified as amended in scattered sections of U.S.C.).

[180] 42 U.S.C. § 262.

[181] Hatch Waxman provision

[182] Price & Rai, *supra* note 9, at 1027.

[183] 42 U.S.C. § 262(k)(7)(A). See also *id.* § 262(k)(7)(B) (prohibiting the FDA from accepting biosimilar applications until four years have passed from the date of the approval of the originator biologic).

[184] See Carver et al., *supra* note **Error! Bookmark not defined.**, at 671(discussing the negotiation process, which with regard to some of the issues covered by the BPCIA took as long as ten years).

[185] In addition to establishing an abbreviated pathway for the licensure of follow-on biologics, the BPCIA also regulates the approval of new biologics and lays out the framework for challenges to patents covering biologics. See, respectively, 42 U.S.C. § 262(a) and § 262(k)(6) (2012). The complexity of the statute has prompted Federal Circuit Judge Lourie to quip that "Winston Churchill once described Russia as a riddle wrapped in a mystery inside an enigma . . . [t]hat is this statute." Amgen v. Sandoz, 794 F.3d 1347, 1351 n.1 (Fed. Cir. 2015).

two different types of follow-on biologics[186] that is substantially different from the Hatch-Waxman generic pathway.[187]

The BPCIA distinguishes between biosimilar and interchangeable follow-on biologics.[188] Sponsors of biosimilars must demonstrate that their product is "highly similar"[189] to the reference product,[190] and that there are "no clinically meaningful differences" between the follow-on and the reference biologic.[191] When applying for a license, sponsors of biosimilars may rely on pre-existing, publicly available data establishing the safety, purity and potency of the reference product.[192] In addition to showing that the biosimilar meets the standards of high similarity and absence of clinically meaningful differences when compared to the reference product,[193] sponsors are required to submit specific information regarding any facilities where the biosimilar is produced, as well as manufacturing processes.[194]

Sponsors of interchangeable follow-on biologics must demonstrate that, in addition to meeting the standards for biosimilarity, their product may be used as a substitute for the reference biologic without "the intervention of the health care provider who prescribed the reference product."[195] In practice, and in line with FDA guidance,[196] the latter requirement means that the interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient."[197]

While the BPCIA was signed into law in 2010, the FDA did not approve a single biosimilar until March 2015.[198] The following year, the Agency approved three biosimilars, followed by five in 2017,[199] including the first biosimilar to be used in the treatment of any type of cancer.[200] In 2018, seven biosimilars were approved, and in 2019 that number climbed to 10.[201] As of January

---

[186] U.S. FOOD & DRUG ADMIN., BIOSIMILAR AND INTERCHANGEABLE PRODUCTS (2017), https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products.

[187] See generally, Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 Fla. St. U. L. Rev. 883 (2017).

[188] 42 U.S.C. § 262(k) (2012).

[189] Id. § 262(i)(2)(A) (2012).

[190] Id. § 262(i)(4) (2012) (defining reference product as a "single biological product" already licensed by the FDA).

[191] Id. § 262(i)(2)(B) (2012).

[192] Id. § 262(k)(2)(A)(iii).

[193] Id. § 262(k)(2)(A)(i)(I)- (IV) (2012).

[194] Id. § 262(k)(2)(A)(i)(V) (2012).

[195] Id. § 262(i)(3) (2012).

[196] U.S. FOOD & DRUG ADMIN., CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT, (2019), https://www.fda.gov/media/124907/download (providing guidance with a focus on therapeutic protein biologics), at 5.

[197] 42 U.S.C. § 262(k)(4)(A)(ii) (2012).

[198] Sandoz, *FDA Approves First Biosimilar Zarxio* (Mar. 6, 2015), https://www.us.sandoz.com/news/media-releases/fda-approves-first-biosimilar-zarxiotm-filgrastimsndz (last accessed Jan. 9, 2020).

[199] U.S. FOOD & DRUG ADMIN., BIOSIMILAR PRODUCT INFORMATION (Jul. 23, 2019), https://www.fda.gov/drugs/biosimilars/biosimilar-product-information (last accessed Jan. 9, 2020).

[200] U.S. FOOD & DRUG ADMIN., FDA APPROVES FIRST BIOSIMILAR FOR THE TREATMENT OF CANCER (Sept. 14, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576112.htm (last accessed Jan. 9, 2020).

[201] U.S. FOOD & DRUG ADMIN., BIOSIMILAR PRODUCT INFORMATION, supra note 199.

2020, there are 26 biosimilars approved by the FDA.[202] To date, no interchangeable follow-on biologic has been approved in the United States.[203]

As biosimilars begin entering the market and compete with biologics, they are expected to translate into savings to patients and the health system in the near future. Estimates, however, vary widely. A study from 2018 calculated that, between 2017 and 2026, direct spending on biologics would decrease by $54 billion as a result of biosimilar competition.[204] Another one, referring to the period between 2014 and 2024, posited that savings generated by the introduction of biosimilars could be as high as $250 billion.[205] A 2019 study put that number back at $60 billion over the next decade.[206]

Even though savings brought about through biosimilar competition are considerable,[207] experts agree that they are very unlikely to be proportionally as high as the ones triggered by the introduction of generics vis-à-vis conventional drugs. Generic competition drives prices down sharply. A recent study on the United States market reported savings of almost $2 trillion attributable to sales of generics in lieu of brand-name drugs between 2009 and 2018.[208] Follow-on biologics, in contrast, are estimated to reduce prices by 10% to 30%.[209] In Europe, where biosimilar competition began years ahead of the United States,[210] early indicators put that number at around 25%. Even though these percentages are substantially lower than discounts introduced by generics, it is worth pointing out that biologics are significantly costlier to manufacturers and pricier to consumers than conventional drugs.[211] As such, relative savings introduced by biosimilar competition should not be overlooked. The following section introduces a case study illustrating this point, focusing on the biologic Humira, which has been the world's best-selling drug in any category for the past seven years.

---

[202] BIOSIMILAR PRODUCT INFORMATION, *supra* note 199.

[203] The FDA finalized guidance on the pathway for expedited review and approval of interchangeable biologic products in mid-2019. See *supra*, note 196.

[204] Andrew W. Mulcahy et al., *Biosimilar Cost Savings in the United States: Initial Experience and Future Potential*, 7 RAND HEALTH Q. 3 (2018) (further noting that the estimated amount is the equivalent of roughly 3% of estimated spending on biologics during the same period).

[205] Express Scripts, *The $250 Billion Potential of Biosimilars* (Apr. 13, 2013) (noting that calculations were based on 11 biosimilar entering the market).

[206] BIOSIMILARS FORUM, STRUCTURAL MARKET CHANGES NEEDED IN U.S. TO ACHIEVE COST-SAVINGS FROM BIOSIMILARS (Mar. 19, 2019), at 3.

[207] See *infra*, Part III.

[208] See e.g. ASS'N. ACCESSIBLE MEDS., 2019 *Generic Drug and Biosimilars Access and Savings in the U.S.*, https://accessiblemeds.org/resources/blog/2019-generic-drug-and-biosimilars-access-savings-us-report (last accessed Jan. 9, 2020).

[209] U.S. FEDERAL TRADE COMM'N, EMERGING HEALTHCARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION [hereinafter EMERGING HEALTHCARE ISSUES] (2009), https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf.

[210] See Mergelin, *infra* note 364.

[211] *Infra*, Part III.

III. PAY-FOR-DELAY DEALS IN THE CONTEXT OF BIOLOGICS

A. A CASE STUDY ON *HUMIRA*

1. The World's Best-Selling Drug

First approved in United States in late 2002,[212] Humira, an anti-inflammatory biologic,[213] has been used in the treatment of a wide array of diseases, including rheumatoid arthritis,[214] certain forms of psoriasis,[215] ulcerative colitis[216] and Crohn's disease.[217]

Humira has often been described as a "miracle drug"[218] and has enjoyed great commercial success.[219] At a time when breakthroughs in the conventional drug space appear increasingly scarce,[220] the popularity of Humira, as well as the relative consensus[221] in the medical literature reviewing it,[222] speak to the current emphasis placed on biologics as the most promising drugs available to patients.

---

[212] U.S. FOOD & DRUG ADMIN., *CBER Approval Letter, Adalimumab (HUMIRA)* (Dec. 31, 2002).

[213] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION (HUMIRA), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125057s232lbl.pdf.

[214] Lynne M. Bang & J. M. Keating, *Adalimumab: A Review of Its Use in Rheumatoid Arthritis*, 18 BIODRUGS 121 (2004).

[215] Eihab A. Alwawi et al., *Treating Psoriasis with Adalimumab*, 4 THERAPEUTIC CLINICAL RISK MGMT. 345 (2008).

[216] William J. Sandborn et al., *Adalimumab Induces and Maintains Clinical Remission in Patients with Moderate-to-severe Ulcerative Colitis*, 142 GASTROENTEROLOGY 257 (2012).

[217] Andrea Cassinotti et al., *Adalimumab for the Treatment of Crohn's Disease*, 2 BIOLOGICS 763 (2008).

[218] Elizabeth Glasure, *A Look at Miracle Drug Humira's Journey to Proven Efficacy*, BIOSPACE (Dec. 5, 2018).

[219] See e.g. Mukherjee, *Protect at All Costs*, *supra* note **Error! Bookmark not defined.** (underscoring the positive impact of Humira across different patient populations). It is nonetheless worth pointing out that Humira's manufacturer (initially Abbott Laboratories and then its spin-off, AbbVie) has been chastised by the FDA for mishandling death complaints related to Humira, and it has also been involved in litigation for failure to warn about certain severe side effects See Ed Silverman, *AbbVie is Reprimanded by the FDA For Failing to Properly Probe Death Complaints*, STAT (Jun. 8, 2018) (noting that Humira was not the only product for which the manufacturer had improperly dealt with death complaints); Tietz v. Abbott Laboratories, (2013) (finding that the manufacturer had failed to warn patients of the risk of lung infection, as well as breach of duty of care under state law for failure to warn physicians about said risk); Delano v. Abbott Labs., 908 F. Supp. 2d (2012) (challenging the manufacturer's failure to update Humira's black-box warning to include information on a certain type of fungal infection, but ultimately dismissed); Murthy v. Abbott Labs, 847 F. Spp. 2d 958 (2012) (claiming failure to warn of a possible association between Humira and heightened risk of certain types of lymphoma, also dismissed for failure to state a claim).

[220] Price & Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, *supra* note 9, at 1026 (noting that "[s]pending on small-molecule drugs is close to stagnant, especially in developed countries").

[221] At least one study has suggested that, given its price point in 2017, Humira was not cost-effective, and that there were at least two competitors that might work better for rheumatoid arthritis. See Jackie Syrop, *Humira Not Cost Effective for RA, ICER Report Concludes*, CENTER FOR BIOSIMILARS (Apr. 11, 2017).

[222] But see *note* 219 and accompanying text.

Since 2012, Humira has been the world's best-selling drug, among conventional drugs and biologics alike,[223] with revenue steadily increasing every year since 2012 through 2019. As of late 2018, Humira had generated life-time sales in excess of $115 billion,[224] and is commercialized in over 60 markets.[225] According to the most recent data, relative to 2018, Humira brought in $19.9 billion in worldwide sales, a number that represents an 8.2% increase from 2017.[226] In 2016, global sales generated $16.1 billion, up from $14.1 billion in 2015, $12.5 billion in 2014, $10.7 billion in 2013 and $9.3 billion in 2012.[227]

While Humira is a blockbuster drug globally, it has derived most of its revenue from the United States market. It also accounts for the majority (60%) of the revenue of its current manufacturer, Chicago-based AbbVie.[228]

The record-shattering revenue generated by Humira is not only a function of its popularity. In addition to the main patent covering its composition, set to expire in late 2016,[229] Humira was at one point covered by over one hundred additional patents,[230] which have largely contributed to giving AbbVie the ability to charge progressively more for Humira. Between 2006 and 2017, the price increased more than threefold, from $16,636 to $58,612 a year.[231] On average, AbbVie raised the price more than 12% a year.[232] In 2014-2015 alone, the price hike was 22%.[233] Calculations indicate that, after rebates, Humira patients currently pay close to $40,000 a year.[234]

The number of patents surrounding Humira has long been the subject of discussion. In a 2015 presentation, AbbVie's CEO, Richard Gonzalez, detailed the company's strategy to protect Humira's "broad patent estate" in the United States,[235] which entailed keeping Humira's intellectual property alive for as long as possible,[236] as well as continuing to pursue new indications

---

[223] Andrew Humphreys, *Top 200 Medicines Annual Report 2019: The King of Medicines*, PHARMA LIVE (Aug. 11, 2019).

[224] Bob Herman, *Humira Sales Approach $20 Billion*, AXIOS (Jan. 25, 2019).

[225] See Mukherjee, *Protect at All Costs*, *supra* note **Error! Bookmark not defined.**.

[226] Herman, *Humira Sales Approach $20 Billion*, supra note 224.

[227] STATISTA, ABBVIE'S REVENUE FROM TOP PRODUCT HUMIRA FROM 2011 TO 2018 (IN MILLION U.S. DOLLARS) (2019), https://www.statista.com/statistics/318206/revenue-of-humira/. The year before it became the world's best-seller drug, Humira generated $7.9 billion in global revenue. Early on, just two years after receiving FDA approval, Humira was generating as much as $2 billion in global revenue, already well above the threshold for a drug to be considered a blockbuster, which is typically seen as $1 billion. See Mukherjee, *Protect at All Costs*, *supra* note **Error! Bookmark not defined.**.

[228] Mukherjeem, *supra* note 227.

[229] U.S. Patent No. 6,090,382 (*Human antibodies that bind human TNFα*) (listing an expiration date of December 31, 2016).

[230] Cynthia Koons, *This Shield of Patents Protects the World's Best-Selling Drug*, BLOOMBERG BUSINESSWEEK (Sept. 7, 2017). To be sure, Humira is not the only biologic with a patent estate in the three digits. Remicade, a biologic manufactured by Janssen (a subsidiary of Johnson & Johnson), which also targets several inflammatory diseases, is another example of this phenomenon. *Id., ib.*

[231] Mukherjeem, *supra* note 227. See also Danny Hakim, *Humira's Best-Selling Drug Formula: Start at a High Price. Go Higher*, N.Y. TIMES (Jan. 6, 2018).

[232] Mukherjeem, *supra* note 227.

[233] ASS'N ACCESSIBLE MED., ENSURING THE FUTURE OF ACCESSIBLE MEDICINES IN THE U.S. (2018), at 14.

[234] See Hakim, *supra* note 231.

[235] Richard Gonzalez, *AbbVie Long-Term Strategy*, ABBVIE (Oct. 30, 2015), at 14-15. See also *infra*, Part III.A.2.

[236] Gonzalez, *AbbVie Long-Term Strategy*, at 13.

for which Humira could gain FDA approval.[237] At the time of Gonzalez's presentation, there were over 70 patents covering Humira set to expire between 2016 and 2034.[238] Crucially, the most significant patent in the estate—the one covering its composition—was set to expire on December 31, 2016 in the United States, thus ushering in the beginning of the end for Humira's patent estate.[239]

Ordinarily, the expiry of the patent covering Humira's composition, combined with a series of challenges to Humira's secondary patents, would have enabled follow-on competitors to start competing with AbbVie immediately after the date of expiry of the composition patent. In fact, the FDA started approving Humira biosimilars in 2016, and it continues to do so, having approved four biosimilars to date.

However, contrary to expectations and to the normal flow of biologic-biosimilar competition, no Humira biosimilars have entered the United States market. Starting in 2017, AbbVie began pursuing a strategy that allows the company to remain the sole manufacturer of Humira in the United States, by entering into agreements with biosimilar manufacturers that effectively delay commercialization of any products competing with Humira until 2023.[240] At the same time, these agreements allow AbbVie's competitors to sell their biosimilars in Europe. The following sections detail the chronology and substance of these agreements, and explain their competition-distorting effects.

2. Anticompetitive Agreements

As seen above, AbbVie's strategy to maintain Humira's market share entails taking advantage of a large patent portfolio while exploring new indications for which Humira might be prescribed. Importantly, AbbVie's intellectual property strategy relies on two fronts: first, the number of staggered patents surrounding Humira; and second, the company's ability to fend off lawsuits challenging the validity of the remaining patents.

From a quantitative perspective, the sheer number of patents related to Humira constitute a thicket that is hard to break. The rate at which AbbVie applied for, and was granted, patents on Humira-related technology spiked in the years prior to the expiry of the composition patent: in 2015 alone, 32 patents issued, followed by 21 in 2016, the last full year in which Humira's composition was patented.[241] Overall, and in the United States alone, AbbVie applied for 247 patents related to Humira technology, 89% of which were submitted to the PTO after receiving FDA approval for its original indication.[242]

From a qualitative perspective, even if some of the patents in the Humira estate were to be deemed invalid, the company is taking advantage of the fact that the invalidation process is time- and resource-consuming. When asked about possible challenges to Humira's secondary patents,

---

[237] *Id.*, 11 and 17.

[238] See Koons, *supra* note 230 (noting that AbbVie's projected duration of Humira's intellectual property amounts to "more than double the protection span a drug such as Humira might normally expect").

[239] See Appendix 1 (providing an overview of Humira's patent estate).

[240] See Appendix 2 (providing a chronology of the settlements).

[241] See Appendix 1.

[242] INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE, Comment Submitted to the Federal Trade Commission, at 2 (further noting that AbbVie applied for over three times more Humira-related patents in the United States than in Europe).

AbbVie's CEO emphasized that "[t]he strategy that we [AbbVie] have in place is not one that hinges on one or two patents."[243]

A salient component of the company's intellectual property management plan consists in adopting a protracted litigation strategy. In 2016, as Humira's composition patent in the United States[244] was coming to an end, and a month before the FDA approved the first Humira biosimilar, AbbVie sued the would-be competitor for infringement of ten Humira-related patents.[245] In the complaint, AbbVie identified an additional 51 patents, but stated that it was not pursuing those as a matter of infringement for the time being.[246] The strategy gave AbbVie the possibility of initiating a different lawsuit at a later time, hence protracting litigation on Humira. If more patents continued to be invalided or expired, or if the biosimilar manufacturer was found not to be infringing on existent patents, AbbVie could then bring another lawsuit, which would in practice prevent the biosimilar from being commercialized in the United States.

This strategy, which lasted just over a year, then morphed into a string of contractual arrangements with would-be competitors that directly sought to shelter Humira from competition in the United States market. On September 28, 2017 AbbVie announced it had entered into an agreement[247] with the manufacturer of the first biosimilar to Humira, an American pharmaceutical company called Amgen.[248] Even though Amgen's biosimilar had been licensed by the FDA to be marketed in the United States,[249] Amgen agreed to delay its commercialization until January 2023. Per the terms of the agreement, Amgen would nonetheless start commercializing the biosimilar in Europe in October 2018.[250] Moreover, Amgen agreed to sell its biosimilar in Europe under a non-exclusive license, which gave AbbVie the ability to pursue additional licensing deals with other biosimilar manufacturers.[251]

In the meantime, the FDA continued to approve biosimilars to Humira. A second biosimilar was approved in 2017,[252] and a third in 2018.[253] A fourth biosimilar was approved in early 2019.[254] Several other biosimilar companies signaled their readiness to enter the market, and several are

---

[243] Koons, *supra* note 230.

[244] In Europe, the patent expired in June 2017. See Generics and Biosimilars Initiative, *Adalimumab Biosimilar Imraldi Makes Waves in Europe* (Feb. 1, 2019), http://gabionline.net/Biosimilars/General/Adalimumab-biosimilar-Imraldi-makes-waves-in-Europe.

[245] See Ed Silverman, *AbbVie and Amgen Lock Horns in the Latest Squabble over Biosimilars*, STAT Magazine (Aug. 8, 2016).

[246] *AbbVie Inc. and AbbVie Biotechnology Ltd. v. Amgen Inc. and Amgen Manufacturing Ltd*. (complaint available at http://www.bigmoleculewatch.com/wp-content/uploads/2016/08/ded-1-99-cv-de431-1.pdf), at 3.

[247] *See* Jessica Dye, *AbbVie Makes Peace with Amgen over Humira Patents*, FINANCIAL TIMES (Sept. 28, 2017) (https://www.ft.com/content/ff1dea83-cbf8-321b-8a59-2fc96158c546).

[248] Amgen manufactures both biologics and biosimilar. CITE https://www.biopharmadive.com/news/7-companies-to-know-in-the-emerging-biosimilars-field/433539/.

[249] Amgen's biosimilar was approved in September 2016, a year before the agreement between AbbVie and Amgen. See Appendix 2.

[250] See Appendix 2.

[251] *Ib.*

[252] Cyltezo, manufactured by Boehringer. See Appendix 2.

[253] Hyrimoz, manufactured by Sandoz. See Appendix 2.

[254] Hadlima, manufactured by Samsung Bioepis. See Appendix 2.

expected to successfully navigate the FDA licensure process in the near future.[255] Again—in theory—the existence of FDA-licensed products should have meant that multiple biosimilars would have entered the market and competed with Humira. That was not the case.

In 2018, AbbVie struck six additional deals with biosimilar manufacturers. As with Amgen's biosimilar, these six would-be competitors agreed not to sell their products in the United States until 2023, but are free to commercialize them immediately in the European market. Two other deals took place in 2019,[256] bringing the total to nine agreements that effectively eliminate competition for Humira in the United States for over five years: the first agreement (with Amgen) was signed on September 28, 2017, with an agreed entry date in the United States market set for January 31, 2023; the remaining entry dates for the other eight biosimilars range between June and December 15, 2023.[257]

As of early 2020, five of the nine biosimilar manufacturers entering into agreements with AbbVie have not obtained FDA approval for their product. Among the ones that have successfully completed the licensure process, one stands out. Sandoz, the manufacturer of a biosimilar to Humira called Hyrimoz, struck a deal with AbbVie on October 11, 2018, agreeing to delay commercialization of the product in the United States until September 30, 2023.[258] The FDA licensed Hyrimoz on October 31, 2018, nearly three weeks *after* the agreement.[259] As a commentator aptly put it, the Agency "gave the green light" in 2018 to a product "that won't be available until 2023."[260] This is not to say that the FDA was wrong in approving the biosimilar—although Part IV will examine the problem from the perspective of the Agency and argue that the FDA *can* and *should* act remedially in situations like this one.[261] Rather, it underscores how industry behavior can not only prolong legally sanctioned monopolies beyond their expected duration, but also deprive permissive gestures from regulatory agencies of their full meaning.[262]

In addition to the anticompetitive nature of the agreements between biologic and biosimilar manufacturers, as well as the outcome of the FDA licensure process, AbbVie's strategy to maintain its stronghold on Humira's commercialization bears direct influence on intellectual property processes, particularly those involving the invalidation of improperly granted patents, a topic that the Article addresses in the following section.

As noted at the end of this Part,[263] the agreements between AbbVie and several biosimilar manufacturers were eventually challenged in mid-2019 on antitrust and consumer protection grounds.[264] But it is important to note here that the first legal challenge to these agreements arose over two years after the key patent on Humira expired. For that period of time, AbbVie retained its monopolistic position in the market, even though the legal mechanisms that initially gave the

---

[255] See Andrew Pollack, *supra* note 169.

[256] Dunn, *AbbVie Completes Humira Sweep*, *supra* note 5.

[257] See Appendix 2.

[258] *Ib.*

[259] *Ib.*

[260] Alex Keown, *FDA Approves Humira Biosimilar That Won't Be Available Until 2023*, BioSpace (Nov. 1, 2018).

[261] *Infra*, Part IV.B.

[262] *Infra*, Part IV.C.3 (arguing that FDA licensure of pharmaceuticals whose sponsors have entered into certain competition-restricting agreements is problematic if the Agency does not have, or does not exercise, the ability to intervene remedially, specifically by revoking the license).

[263] *Infra*, Part IV.

[264] UFCW Local 1500 Welfare Fund v. AbbVie Complaint, *infra*, note 296.

company the power to exclude competitors were no longer present. The next section briefly explores the consequences of this lack of legal interventions.

3. Consequences of Anticompetitive Agreements

In 2018, AbbVie increased the price of Humira by 9.7%.[265] The following year, there was a price hike of 6.2%.[266] And in January 2020 AbbVie again raised the price by more than 7%.[267] While Humira price hikes have long occurred on a yearly basis,[268] 2018 marked the first time that AbbVie increased the price after entering into the first of its agreements with biosimilar manufacturers. At that point, the main patent covering Humira had been expired for at least a year.[269] Keeping in mind that Humira is currently priced at close to $40,000 per year after rebates, or $50,000 if there are none,[270] the post-patent absence of competition poses very serious economic consequences for patients, as well as for the healthcare system. One study, for instance, has estimated that the 9.7% increase in 2018 will have added $1.2 billion in costs to the healthcare system in the United States.[271]

As Humira's patent protection began thinning out in late 2016, worldwide sales began declining. Data pertaining to the first quarter of 2019 show that global sales of Humira decreased by 5.6%.[272] That decline, however, is due to biosimilar competition outside the United States. Starting in 2018, the same biosimilar that companies agreed not to commercialize in the United States began entering the European market, as per the terms of the agreements with AbbVie.[273]

In Europe, the uptake of biosimilars was quick. Take the case of Imraldi, the fourth biosimilar to Humira approved by the FDA in the United States.[274] Imraldi was approved by the European Commission in August 2018 and reached the market the following October.[275] By November, it had acquired 62% of market share in Germany,[276] which has traditionally been Humira's largest European market.[277]

---

[265] ENSURING THE FUTURE OF ACCESSIBLE MEDICINES, at 12.

[266] Bob Herman, *2019's Drug Price Hikes Are Here*, AXIOS (Jan. 2, 2019).

[267] Miachel Erman, *More January U.S. Price Hikes Take 2020 Tally to Over 330 Drugs with Higher Cost*, REUTERS (Jan. 2, 2020), https://www.reuters.com/article/us-usa-healthcare-drugpricing/more-january-u-s-price-hikes-take-2020-tally-to-over-330-drugs-with-higher-cost-idUSKBN1Z11C9 (last accessed January 2, 2020).

[268] This phenomenon raises questions in itself, although outside the scope of this Article.

[269] *Supra*, note 239.

[270] *See* Andrew Pollack, *supra* note 169.

[271] Jackie Syrop, *Latest Humira Price Increase Could Add $1 Billion to US Healthcare System in 2018*, CENTER FOR BIOSIMILARS (Jan. 5, 2018) (noting that the calculations were based on Humira's revenue generated in the United States market, which at the time was averaging $12.6 billion per year).

[272] Mukherjeem, *supra* note 227.

[273] See Alex Keown, *Dissimilar to U.S. Market, Humira Biosimilar Competition Launches in Europe*, BioSpace (Oct. 16, 2018).

[274] See Appendix 2.

[275] *Supra*, note 244.

[276] *Id., ib.*

[277] *Id., ib.* (reporting that, in the year prior to facing biosimilar competition, sales in Germany accounted for 28% of Humira's European market).

The first four biosimilars to Humira launched in Europe in October 2018.[278] As a result, prices came down 10% to 80% across Europe[279] when compared to those charged by AbbVie for Humira before facing biosimilar competition. Scandinavia registered the steepest discounts,[280] while countries like the United Kingdom saw variation in the range of 15% to 35%.[281]

As a result of biosimilar competition, AbbVie itself has lowered the price of Humira in Europe, both to preserve a modicum of market share, and to comply with varying pricing rules set by national authorities.[282] As with its competitors in Europe, AbbVie's discounts span the range of 10% to 80%, with AbbVie's CEO stating in late 2018 that "discounting has been on the higher end."[283]

Put simply, the biological product needed by patients taking Humira in the United States is supplied at often deeply discounted prices in the European market, with discounts being offered, among others, by the same company that charges increasingly higher prices to American consumers.

The first set of problems are thus of economic nature, resulting in unfair treatment of consumers—who are also patients—in the United States. Additionally, suppressing competition in a market already distorted by patent and regulatory exclusivities raises questions from the perspective of innovation policy. The prolongment of AbbVie's de facto monopoly circumvents the legal architecture of R&D incentives in the biopharmaceutical arena. AbbVie's market position is extended through contractual fiat even *after* the statutory market-distorting, innovation-enhancing[284] distortions to the market have ended.

Moreover, there are systemic consequences likely to stretch beyond the realm of Humira. AbbVie's strategy may operate as a blueprint in the future for large biologic manufacturers wishing to preserve post-patent and post-exclusivity market share. As a consequence, there might be fewer challenges to secondary patents, among which there is a greater likelihood of weaknesses affecting patent validity. The first agreement pursued by AbbVie, with biosimilar manufacturer Amgen, happened on the heels of patent challenges—and it functioned precisely as a challenge stopper.

Additional challenges to Humira's patent estate, brought by other biosimilar manufacturers, also came to a halt as AbbVie entered into these agreements. Take the case of Californian biosimilar manufacturer Coherus, which challenged several patents covering Humira's dosing regimen in 2016.[285] The Patent Trial and Appeal Board (PTAB) at the Patent and

---

[278] See Ned Pagliarulo, *Humira Biosimilars Launch in Europe, Testing AbbVie*, BIOPHARMADIVE (Oct. 17, 2018).

[279] See Susan Ladika, *Bringing Humira (Its Price) Down a Peg*, MANAGED CARE (Jan. 25, 2019).

[280] Zachary Brennan, *AbbVie Sees 80% Discounts in Nordic Market with New Humira Biosimilars*, RAPS (Nov. 2, 2018).

[281] Ned Pagliarulo, *supra* note 278.

[282] See Samantha DiGrande, *Are Rumors of AbbVie's Humira Price Cuts What They Seem?*, CTR. BIOSIMILARS (Nov. 2, 2018) (noting that several European countries have rules in place that require the manufacturer of the reference product to lower its price, or match that of competitors, after biosimilars enter the market).

[283] Brennan, *supra* note 280.

[284] Patents and regulatory exclusivities have long been understood as interventions designed to promote innovation. See *supra* note 70. This Article is agnostic on this proposition, merely noting that the goal of promoting innovation is not being supported by current industry practices, some of which have gone unchecked for significant periods of time.

[285] See Anne Steele, *Patent Office to Review a Regimen of AbbVie's Humira*, WALL ST. J. (May 17, 2016).

Trademark Office struck the patents down in 2017.[286] In January 2019, Coherus entered into an agreement with AbbVie, agreeing to delay commercialization of its biosimilar to Humira until 2023 in the United States, while marketing it non-exclusively in other markets, as well to cease all intellectual property litigation related to Humira.[287] A few months later, Boehringer Ingelheim, a German manufacturer whose biosimilar to Humira had gained FDA approval in 2017, entered into a similar agreement with AbbVie, including the obligation to drop all challenges to Humira's patent estate.[288] Boehringer was the ninth and outstanding would-be competitor settling with AbbVie.[289] With this final agreement, all patent challenges to Humira came to an end.

The opportunity cost of stopping these patent challenges might never be fully appreciated. Ongoing litigation was based on secondary patents, some of which were challenged and invalidated. As a result of the plethora of agreements AbbVie entered into, courts and adjudicatory bodies are now unlikely to have the opportunity to review other potentially weak or unworthy patents still active in Humira's estate.

Collectively, the problems referenced in this section stem from an entity-specific behavior as the patent landscape for many blockbuster biologics undergoes significant changes. However, it is important to note that Humira is not an isolated case when it comes to surrounding a drug with thickets of patents. A report surveying the top 12-grossing drugs in the United States found that there is an average of 125 patent applications filed per drug, with an average of 71 patents granted per drug.[290] Similarly, price increases among blockbuster drugs are the norm. Since 2012, only one of these 12 drugs has decreased in price, while collectively prices have increased by 68%.[291] All of these drugs, like Humira, have been on the market for well over a decade.[292] The precedent set by AbbVie's string of anticompetitive agreements, if left unchecked, offers an easily replicable strategy for future competition-restricting behaviors by manufacturers of biologics wishing to preserve their exclusionary power in the post-patent world at the expense of patient populations.

4. Lawsuits Challenging the Validity of Pay-for-Delay Deals

---

[286] FDA NEWS, *PTAB Invalidates AbbVie's Humira Dosing Patent — Again* (Jul. 11, 2017), https://www.fdanews.com/articles/182553-ptab-invalidates-abbvies-humira-dosing-patent-again.

[287] BIOSIMILAR DEVELOPMENT, *Coherus BioSciences Announces Global Settlement with AbbVie Securing Rights To Commercialize Its Adalimumab Biosimilar Candidate, CHS-1420* (Jan. 25, 2019), https://www.biosimilardevelopment.com/doc/coherus-biosciences-announces-global-settlement-candidate-0001.

[288] CTR. BIOSIMILARS, *AbbVie and Boehringer Ingelheim Settle Over Biosimilar Adalimumab* (May 14, 2019), https://www.centerforbiosimilars.com/news/abbvie-and-boehringer-ingelheim-settle-over-biosimilar-adalimumab. See also AbbVie Inc. v. Boehringer Ingelheim Int'l GMBH, Case No. 1:17-cv-1065 (D. Del.), Boehringer's Answer, Defenses, and Counterclaims (Doc. 20, Sept. 11, 2017), at 41-45 (listing Boehringer's contentions, prior to settlement, that several of Humira's secondary patents were weak, "derived from the prior art" and "do not represent innovation").

[289] *Id., ib.*

[290] IMAK, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PHARMACEUTICAL PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES (2018), at 4.

[291] *Id.*, at 4.

[292] *Id., ib.*

The validity of the agreements to delay the entrance of Humira competitors in the United States market was eventually challenged in the first half of 2019.[293] As of early 2020, there are six lawsuits targeting AbbVie and the biosimilar companies involved in these deals.[294]

On March 18, UFCW Local 1500 Welfare Fund, a New York-based employee welfare benefits fund,[295] initiated a putative class action lawsuit[296] claiming that AbbVie engaged in "unlawful market division agreements" to keep Humira competition at bay until 2023.[297] Reiterating claims by the biosimilar companies who had previously challenged some of Humira's secondary patents,[298] the lawsuit emphasizes the weakness of many secondary patents covering Humira,[299] and contends that AbbVie leveraged Humira's patent thicket to delay biosimilar competition in the Unites States from 2017 onwards.[300] The complaint asserts that the agreements are anticompetitive as they result in an "unlawful market division" between Europe and the United States.[301] Further, it notes that the duality in patent litigation strategy in the European and United States markets underscores the anticompetitive nature of these agreements:

> As in the U.S., AbbVie had Humira patent protection in Europe. But AbbVie ceded the European market to biosimilar competition—despite that patent protection—in exchange for maintaining its monopoly in the U.S. (…) This trade-off meant that the lower price for Humira in Europe was subsidized by the much higher price in the United States where AbbVie unlawfully maintained its monopoly.[302]

UFCW claims that AbbVie and the manufacturers of biosimilars to Humira entered into unlawful market division agreements in violation of the Sherman Act.[303] The complaint further claims that AbbVie engaged in monopolization[304] by unduly keeping a 100% market share for adalimumab (the active ingredient in Humira) in violation of federal antitrust law,[305] as well as multiple state laws;[306] that AbbVie and the biosimilar manufacturers engaged in conspiracy and

---

[293] Susannah Luthi, *AbbVie Sued Over Humira 'Patent Thicket,'* MODERN HEALTHCARE (Mar. 19, 2019).

[294] Zachary Brennan, *Six Lawsuits Target AbbVie's Humira and its Patent Thicket*, RAPS (Apr. 2, 2019).

[295] *Id.*, at 9.

[296] UFCW Local 1500 Welfare Fund v. AbbVie Inc. et al., [hereinafter UFCW Complaint], at 30-31.

[297] *Id.*, at 5.

[298] *Supra* note 288, and accompanying text.

[299] UFCW Complaint, at 21-22.

[300] *Id.*, at 22.

[301] *Id., ib.*

[302] *Id.,* at 22-23 and 3.

[303] *Id.,* at 34-35 (arguing that the agreements constitute a *per se* violation of 15 U.S.C. § 1 and, alternatively, that a rule of reason analysis would still indicate that the agreements were violative of federal antitrust laws, given the revenue that the biosimilar manufacturers stand to gain from sales in the European market).

[304] *Id.,* at 48-50. See also 15 U.S.C. § 2.

[305] *Id.,* at 49.

[306] *Id.,* at 55-54. See, *inter alia*, Ariz. Rev. Stat. §§ 44-1401, et seq.; Conn. Gen. Stat. § 35-24, et seq.; N.C. Gen. Stat. §§ 75-1, et seq.; Vt. Stat. Ann. 9, §§ 2453, et seq.

combination in restraint of trade under multiple state laws;[307] and that all parties to the agreements violated principles of unjust enrichment in multiple states by overcharging members of the class action.[308]

Four days after the UFCW complaint was entered, the City of Baltimore initiated a separate putative class action against AbbVie and only the first of the biosimilar companies to enter into a settlement, Amgen.[309] Four other putative class actions started around the same period.[310]

While the outcome of these lawsuits may break AbbVie's monopoly in the United States and infuse the market with more affordable alternatives to Humira, it is important to note that more than two years had passed from the expiration of the main patent on Humira when the first lawsuit was brought against AbbVie,[311] and over a year and half from the first settlement, between AbbVie and Amgen.[312] If these class actions were to succeed, additional time would go by. For Humira patients in the United States, the interim period is far too long, and available remedies are unlikely to fully account for the supra-competitive prices these patients have been paying since patent expiration and FDA approval of biosimilars to Humira.[313]

In theory, the law has the appropriate mechanisms to scrutinize potentially anticompetitive behavior, as well as to curb and penalize it, with antitrust frameworks at the forefront of this scrutiny. In practice, however, antitrust mechanisms tend to offer temporally protracted responses in situations like the one addressed in the Humira case study.

Keeping in line with these propositions, the Article next offers a brief description of the antitrust framework applicable to pay-for-delay deals, and argues that, *in addition* to antitrust, another type of legal intervention is required to address these types of anticompetitive behaviors in an expeditious fashion.

B. The Antitrust Framework to Address Pay-for-Delay Deals

The practice of delaying competition through settlements is not new, even though AbbVie was the first company to employ this strategy in the context of biologic-biosimilar competition. The Article now provides an overview of similar behaviors in previous situations, involving manufacturers of conventional drugs and their generic competitors, and briefly explains how the antitrust principles governing these settlements are transferable to the context of biologic-biosimilar competition.

1. Pay-for-Delay in the Pre-Biologics Era

---

[307] *Id.,* at 50-54. See, *inter alia*, Cal. Bus. Code §§ 16700, et seq.; Hawaii Code § 480, et seq.; 740 Ill. Comp. Stat. Ann. 10 / 3, et seq.; N.Y. Gen. Bus. L. §§ 340, et seq.; Wis. Stat. §§ 133.03, et seq.

[308] *Id.,* at 62-82.

[309] Mayor and City Council of Baltimore v. AbbVie Inc., AbbVie Biotechnology Ltd., and Amgen Inc.

[310] See Miami Fraternal Order of Police vs AbbVie; Pipe Trades Services MN Welfare Fund vs AbbVie; St Paul Electrical Workers' Health Plan vs AbbVie; Welfare Plan of the International Union of Operating Engineers Locals v. AbbVie (all putative class actions naming only Amgen as co-defendant).

[311] See Appendix 2.

[312] *Ib.*

[313] The same arguments hold true for the supra-competitive costs supported by the United States health system during the same period of time.

As seen in Part I, the abbreviated regulatory pathway introduced by the Hatch-Waxman Act was designed to enable generic competitors to enter markets as soon as relevant patents expired or were successfully challenged.[314] In previous situations, the equilibrium between patent protection and second-comer competition was often disrupted by agreements between the manufacturer of a conventional drug and its would-be generic competitor. These agreements, which became known as "exclusion," "reverse" or "pay-for-delay" settlements,[315] came to the attention of the Federal Trade Commission (FTC) in 2000, precisely when the first wave of patent term expirations for blockbuster small-molecule drugs began unfolding.

In *FTC v. Actavis*, the landmark 2013 case on pharmaceutical pay-for-delay settlements,[316] the Supreme Court delineated the structure of these agreements as follows:

> Company A sues Company B for patent infringement. The two companies settle under terms that require (1) Company B, the claimed infringer, not to produce the patented product until the patent's term expires, and (2) Company A, the patentee, to pay B many millions of dollars. Because the settlement requires the patentee to pay the alleged infringer, rather than the other way around, this kind of settlement agreement is often called a "reverse payment" settlement agreement.[317]

Throughout the 2000s—and between the first and second waves of en masse expiration of pharmaceutical patents—pay-for-delay became an increasingly popular strategy in the pharmaceutical industry. The number of potential pay-for-delay settlements monitored by the FTC rose from 3 in 2005 to 40 in 2012.[318] In 2013, the FTC estimated that pay-for-delay was costing consumers in the United States an average of $3.5 billion per year.[319]

The classic pay-for-delay scheme is embodied in *Actavis*. The case involved AndroGel, a form of synthetic testosterone manufactured by Solvay Pharmaceuticals.[320] Generic drug manufacturers, including Actavis, filed an abbreviated new drug application with the FDA, certifying that the AndroGel formulation patent[321] listed in the Agency's Orange Book was invalid

---

[314] *Supra*, notes 77.

[315] U.S. FED. TRADE COMM'N, PREPARED STATEMENT OF THE FEDERAL TRADE COMMISSION BEFORE THE UNITED STATES SENATE COMMITTEE ON THE JUDICIARY, SUBCOMMITTEE ON ANTITRUST, COMPETITION POLICY AND CONSUMER RIGHTS ON PAY-FOR-DELAY DEALS: LIMITING COMPETITION AND COSTING CONSUMERS [hereinafter 2013 FTC STATEMENT] (Jul. 23, 2013), at 1.

[316] *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013) [hereinafter *Actavis*].

[317] *Actavis,* at 2227.

[318] 2013 FTC STATEMENT, supra note 315, at 4. The year 2012 constitutes a relevant marker in this chronology, as it was the year in which the Supreme Court first addressed pay-for-delay in the context of pharmaceuticals. *Infra*, ACTAVIS.

[319] U.S. FED. TRADE COMM'N, STATEMENT OF CHAIRWOMAN EDITH RAMIREZ, COMMITTEE ON THE JUDICIARY SUBCOMMITTEE ON ANTITRUST, COMPETITION POLICY & CONSUMER RIGHTS, U.S. SENATE (Jul. 23, 2013), at 1 (further noting the detrimental economic impact of these settlements on governmental health programs like Medicare and Medicaid). See also Herbert Hovenkamp, *Anticompetitive Patent Settlements and the Supreme Court's Actavis Decision* [hereinafter *Anticompetitive Patent Settlements*], 15 Minn. J.L. Sci. & Tech. 3, 10 (2014) (noting that, under a pay-for-delay agreement, "[f]ormally, consumer welfare remains the same as it would be under continued monopoly production by a single firm.").

[320] U.S. FOOD & DRUG ADMIN., ANDROGEL, https://www.fda.gov/media/80632/download.

[321] U.S. PATENT 6,503,894 (covering AndroGel's formulation; AndroGel's composition was not patented).

and that no patent infringement would occur upon commercialization of their generic products.[322] Solvay sued the generic companies.[323] After thirty months, and per Hatch-Waxman rules, the FDA approved Actavis' first-to-file application in the pendency of patent litigation.[324] Instead of entering the market, Actavis (and other generic companies) settled with Solvay in 2006, agreeing to delay commercialization until 2015 in exchange for large sums of money.[325] In the case of Actavis, the amount was estimated to range between $19 million and $30 million annually.[326]

In 2009, the FTC filed a complaint claiming multiple violations of the Sherman and FTC Acts.[327] The FTC noted that "by deferring competition, the parties would preserve monopoly rents that would be shared amongst them – at the expense of the consumer savings that would result from price competition."[328] Both the district and the Eleventh Circuit, however, dismissed the complaint.[329] The Eleventh Circuit ruled in 2012 that pay-for-delay agreements were "immune from antitrust attack so long as its anticompetitive effects fall within the scope of the exclusionary potential of the patent."[330] The following year, the Supreme Court held pay-for-delay behavior "can sometimes violate the antitrust laws" and therefore the complaint should have been allowed to proceed.[331]

2. The Actavis Framework for Pay-for-Delay Agreements

In 2013, the Supreme Court took the view in *Actavis* that large and otherwise unjustified payments flowing from a pharmaceutical company to would-be competitors "can bring the risk of significant anticompetitive effects."[332] Pay-for-delay agreements are thus subject to antitrust scrutiny.[333] Further, *Actavis* held that the antitrust analysis is separate from, and does not have to probe into, the validity of the patents associated with the drug in question.[334]

The Court also determined that a rule-of-reason framework governs the antitrust analysis.[335] This determination was contrary to the FTC's contention that pay-for-delay deals were presumptively unlawful.[336] The Court reasoned that

---

[322] *Actavis*, at 2229.

[323] *Actavis*, *ib.*

[324] *Id.*, *ib.*

[325] *Id.*, *ib.*

[326] *Id.*, *ib.*

[327] U.S. FED. TRADE COMM'N, CIVIL COMPLAINT, at 27-28.

[328] *Id.*, at 14.

[329] *Actavis*, at 2227.

[330] *FTC v. Watson Pharms., Inc.*, 677 F.3d 1298, 1312 (2012).

[331] *Actavis*, at 2227.

[332] *Id.*, at 2236.

[333] *Id.*, at 2237.

[334] *Id.*, at 2230-31; Hovenkamp, *Anticompetitive Patent Settlements*, *supra* note **Error! Bookmark not defined.**, at 5.

[335] *Actavis*, *supra* note 317, at 2231. See also Herbert Hovenkamp, *The Rule of Reason*, 70 FLA. L. REV 81, 83 (2018) (defining "rule of reason" as one that "requires the plaintiff to plead and prove that defendants with market power have engaged in anticompetitive conduct").

[336] *Actavis*, at 2237.

> the likelihood of a reverse payment bringing about anticompetitive effects depends upon its size, its scale in relation to the payor's anticipated future litigation costs, its independence from other services for which it might represent payment, and the lack of any other convincing justification. The existence and degree of any anticompetitive consequence may also vary as among industries.[337]

While the *Actavis* framework dealt with potentially anticompetitive practices involving cash payments, both pre- and post-*Actavis* case law indicate that other types of behavior in pay-for-delay deals can amount to anticompetitive behavior. For instance, in *Palmer v. BRG*, the Supreme Court ruled in 1990 that an agreement between competitors to cease competing could be considered "anticompetitive regardless of whether the parties split a market within which both do business or whether they merely reserve one market for one and another for the other."[338] Since *Actavis*, courts have directly addressed the problem of in-kind or non-cash payments.[339] In 2016, for example, the First Circuit in *In re Loestrin* reversed a district court ruling interpreting *Actavis* to apply only to monetary payments.[340] And, in *King Drug Co. of Florence*, the Third Circuit analyzed a case in which "payment" consisted of early entrance into the market for chewable anticonvulsant drugs, coupled with the brand-name manufacturer's promise not to produce its own generic version of the drug, and held that such a combo met the *Actavis* threshold.[341] As the court put it, even in cases in which consideration is not purely monetary

> an unusual, unexplained reverse transfer of considerable value from the patentee to the alleged infringer (…) may (…) give rise to the inference that it is a payment to eliminate the risk of competition.[342]

In spite of occasional misapplications at the lower court level,[343] *Actavis* is widely seen as a turning point in the field of pharmaceutical competition. Since *Actavis* was decided, the number of pay-for-delay deals has decreased.[344]

Even though *Actavis* was decided with reference to conventional drugs, there is no reason not to apply Actavis to biologics on account of the structural differences between the two types of drugs.[345] In the context of biologic-biosimilar competition, the skeletal elements of pay-for-delay remain the same as the ones enunciated by the *Actavis* court, as seen in the Humira case study above.[346] There are, however, characteristics innate to antitrust interventions that render the current legal framework for curbing anticompetitive behaviors an unwieldy and often ineffective response

---

[337] *Id.*, *ib.*

[338] *Palmer v. BRG of Ga.*, Inc., 498 U.S. 46, 49-50 (1990).

[339] See Michael Carrier, *Payment After Actavis*, 100 IOWA L. REV. 7 (2014) (analyzing non-cash forms of consideration in pay-for-delay deals).

[340] *In re Loestrin* 24 Fe Antitrust Litig., 814 F.3d 538, 542 (2016).

[341] *King Drug Co. of Florence v. Smithkline Beecham Corp.*, 791 F.3d 388 (3d Cir. 2015).

[342] *Id.*, at 394.

[343] See Michael Carrier, *How Not to Apply Actavis*, 109 NW. U. L. REV. COLLOQUY (2014) (criticizing district court rulings in *In Re Lamictal* and *In re Loestrin* for misapplication of the Actavis framework).

[344] Michael Carrier, *FTC v. Actavis: Where We Stand After 5 Years*, IP WATCHDOG (Jun. 18, 2018) (suggesting that antitrust scrutiny has functioned as a deterrent to pay-for-delay agreements).

[345] Carrier & Minniti, *Biologics: The New Antitrust Frontier*, *supra* note 12, at 24 ("regulation under the BPCIA easily offers sufficient similarities to the Hatch-Waxman Act to allow application of *Actavis*'s broad principles").

[346] *Supra*, Part III.A.

to the harms caused to patients and health systems by pay-for-delay agreements between pharmaceutical companies. The Article now turns to the downside of reliance on antitrust frameworks to curb these behaviors, with a particular focus on the detrimental effects it poses to biologic-biosimilar competition as patent protection for the formers thins out.

3. Shortcomings of the Antitrust Framework

No single branch of law aseptically regulates competitive behaviors in markets for pharmaceutical drugs. As Michael Carrier and Carl Minniti have observed, this is a field in which antitrust, patent law and a heterogenous body of regulations intersect with extra-legal factors,[347] ranging from economics to public policy.[348] Yet, from a perspective of addressing potentially anticompetitive occurrences, antitrust remains the primary legal tool for dealing with issues like those presented by pay-for-delay deals.[349]

Responses offered by the application of antitrust principles, however, have to contend with several problems, from overreliance on concepts of efficiency to definitional problems posed by the concept of market power.[350] In the pharmaceutical arena in particular, the application of antitrust law is further complicated by the complexity of markets and regulatory regimes.[351] Moreover, underlying the specificities of pharmaceutical antitrust, is the temporal nature of antitrust interventions in cases like pay-for-delay: *Actavis* offers the possibility of *ex post* scrutiny, but that scrutiny is bound to take place after a significant period of time—and consequently of potentially protracted harmful behavior affecting patients in need of biopharmaceutical products. The case study on Humira illustrated this shortcoming of the remedial facet of antitrust: while the FDA approved the first biosimilar to Humira in 2016, anticipating a 2017 market entrance,[352] it was not until March 2019 that the first antitrust lawsuits were brought.[353] Similarly, there was a

---

[347] Carrier & Minniti, *supra* note 12, at 3 (noting that "[t]he pharmaceutical industry lies at the intersection of patent law, antitrust law, federal and state regulations, and complex markets"). See also Patricia M. Danzon, *Competition and Antitrust Issues in the Pharmaceutical Industry*, Report to the Regional Competition Center for Latin America (2014), at 3.

[348] See generally STUART O. SCHWEITZER & Z. JOHN LU, PHARMACEUTICAL ECONOMICS AND POLICY: PERSPECTIVES, PROMISES, AND PROBLEMS (2018); Frederic M. Scherer, *Pharmaceutical Innovation*, in HANDBOOK ECON. OF INNOVATION, BRONWYN H. HALL & NATHAN ROSENBERG, EDS. (2010); Michael Carrier, *Two Puzzles Resolved: Of the Schumpeter - Arrow Stalemate and Pharmaceutical Innovation Markets*, 93 IOWA L. REV. 393 (2008).

[349] PHILLIP E. AREEDA & HERBERT HOVENKAMP, FUNDAMENTALS OF ANTITRUST LAW (4th edition). See also Eleanor M. Fox, *Modernization of Antitrust: A New Equilibrium*, 66 CORNELL L. REV. 1140, 1182 (1981) (framing the role of antitrust law as promoting multiple goals, among which the "protection of the competition process as market governor").

[350] See e.g. RICHARD POSNER, ANTITRUST LAW (1976) (arguing for an efficiency-centric approach to antitrust regulation); Fox, *supra* note 349, at 1176-1177 (surveying the centrality of efficiency arguments in antitrust scholarship); Louis Kaplow, *On the Relevance of Market Power*, 130 HARV. L. REV 1303, 1305 (2017) (exploring the multiple functions of market power in competition law and policy). For a general critique of current antitrust law, see TIM WU, THE CURSE OF BIGNESS: ANTITRUST IN THE NEW GILDED AGE (2018).

[351] See Michael Carrier, *Three Challenges for Pharmaceutical Antitrust*, 59 SANTA CLARA L. REV. __ (forthcoming 2019).

[352] *Supra*, note 249 and accompanying text.

[353] *Supra*, Part III.A.4.

time lag in previous pay-for-delay deals: the *Actavis* settlement took place in 2006, but it took almost three years for the FTC to initiate litigation against the parties involved in the deal.[354]

The delayed nature of antitrust responses is of heightened relevance in the context of pay-for-delay involving biologic products for two reasons. First, the reference drugs affected by the ongoing wave of patent expirations, both presently and in the foreseeable future, are among the most promising available to patients suffering from serious diseases,[355] including several types of cancers, multiple sclerosis, diabetes, asthma and different forms of arthritis.[356] And second, these drugs are some of the most expensive ever to come to the United States market.[357] Maintaining artificially high prices in the post-patent, post-exclusivity market generates detrimental effects of a magnitude that patients and health systems had not experienced before.

The final section of the Article links this magnitude of detrimental effects to the need for regulatory interventions to curb pay-for-delay *outside* the realm of antitrust. It explains why antitrust law and antitrust regulators should not be the sole players tasked with corrective functions in cases of pay-for-delay. Expanding on this idea, the Article argues for a greater *ex post* role for a different regulator with institutional, statutory and policy capacity to influence competitive behaviors—the FDA.

IV. BEYOND ANTITRUST: A NOVEL SOLUTION FOR ADDRESSING ANTICOMPETITIVE BEHAVIOR

So far, this Article has described the challenges faced by the branch of the law specifically designed to address anticompetitive behaviors in responding to pay-for-delay. It now turns to a solution outside the realm of antitrust that could serve as a deterrent for this type of behaviors: it argues that the FDA is well placed to address some of the failures that currently plague biosimilar competition. It posits that, by granting licenses that result in no product commercialization, FDA's role as an administrative agency is reduced to empty gesture. This Part shows that the FDA has both the statutory authority and the obligation to revoke biosimilar licenses in cases of pay-for-delay. This solution is also consistent with policy goals: given the Agency's role as a locus for innovation policy, the FDA *should* apply the licensing revocation framework to cases of pay-for-delay as a way to encourage motivated manufacturers to seek regulatory approval for their products, while compelling inactive players to clear the field for legitimate competition.

Part A summarizes the need for regulatory interventions outside the field of antitrust in order to address pay-for-delay in the context of biologic-biosimilar competition. Part B makes the case that the FDA is institutionally well placed to address the problem. Part C argues that, as a matter of statutory interpretation, the FDA *can* and *should* revoke biosimilar licenses when manufacturers fail to produce the approve product within a reasonable timeframe. Part C also outlines the proposed regime, detailing its mechanics and possible forms of implementation, as

---

[354] *Actavis*, at 2290.

[355] See Bahija Jallal, *Realizing the Promise of Biologics*, *supra* note 165 (observing that "[t]he future of biologics and its growing potential to benefit patients with unmet medical needs has perhaps never been more promising"); see also *supra* note 171 and accompanying text (emphasizing the high cost of the latest generation of gene therapies).

[356] Jallal, *supra* note 165; see also H.A. Daniel Lagassé et al., *Recent Advances in (Therapeutic Protein) Drug Development*, F1000Research (Feb. 7, 2017) (exemplifying the growing domains into which biologic research and applications are expanding).

[357] *Supra*, Part II.A.

well as exploring the advantages and drawbacks of license revocation with regard to biosimilar competition.

A. THE NEED FOR CUMULATIVE REGULATORY INTERVENTIONS IN THE DRUG PATENT ECOSYSTEM

As seen above, the current wave of patent expirations is different from the previous ones because it affects a type of drug that was relatively rare until the twenty-first century.[358] In addition to their immediate applications and future promise, biologics come at a price tag significantly higher than that of conventional drugs. Some commentators have observed that the price savings attributable to biosimilar competition are more "modest" than those triggered by generic competition in the conventional drug space.[359] Generic versions of conventional drugs translate into savings in the 80% range, both in the United States and Europe.[360] Due to manufacturing constraints[361] and costlier regulatory review when compared to generics,[362] the European market[363] has registered savings in connection with the introduction of biosimilars that are relatively lower: one study estimated average saving across European Union countries at around 25%.[364]

While this is a relevant component of the economics of biosimilar competition, an important element is missing from this analysis: aggregate savings from biosimilars are not insignificant. Even when taking only into account the average biosimilar discount in the European market, saving a quarter of the price of a biologic is not negligible from the perspective of patients, insurers and health systems. Moreover, as seen in the case of Humira, in some cases biosimilar competition has triggered discounts of as little as 10% and as high as 80% in different European countries.[365] Bearing in mind that Humira has a price tag of $38,000 per year after rebates,[366] the positive social welfare impact of *actual* biosimilar competition in the United States market should not be minimized. As a report from the FTC has put it

> [a]lthough not as steep a discount as small-molecule generic drugs, a 10 to 30 percent discount on a $48,000 drug product represents substantial consumer savings.[367]

---

[358] Haydon, *Biologics: The Pricey Drugs Transforming Medicine*, *supra* note 10.

[359] Price & Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, *supra* note 9, at 1028 (referencing data from the European market).

[360] See Matthew Solan, *Buying into Generic Drugs*, HARV. HEALTH BLOG (Jul. 25, 2016). See also Panos Kanavos, *Do Generics Offer Significant Savings to the U.K. National Health Service?*, 23 CURR. MED. RES. OPIN. 103 (2007) (reporting savings on selected generics exceeding the 90% threshold in the United Kingdom).

[361] Price & Rai, *supra* note 9, at 1028.

[362] Henry G. Grabowski et al., *Regulatory and Cost Barriers Are Likely to Limit Biosimilar Development And Expected Savings In The Near Future*, HEALTH AFF. (2004).

[363] The European market is widely seen as the "global pioneer" in the introduction of biosimilars, which is why it often used as the benchmark in this field. See Cécile Rémuzat et al., *Key Drivers for Market Penetration of Biosimilars in Europe*, 5 J. MARKET ACCESS & HEALTH POL'Y 1, 1 (2017).

[364] Francis Mergelin et al, *Biosimilars and the European Experience: Implications for the United States*, 32 HEALTH AFF. 1803 (2013).

[365] *Supra*, note 279.

[366] Or close to $50,000 if there are no rebates. *Supra*, Part III.A.

[367] See EMERGING HEALTHCARE ISSUES, *supra* note 209, at v.

In addition to differences related to the economics of biosimilar competition, the current landscape is also distinctive because patent thickets have grown worse.[368] The case study on Humira does not portray an isolated phenomenon. Data show that the manufacturers of the eight largest-grossing biologics in the United States applied for an average of 151 patents related to the biologic, with 80% of the applications occurring after FDA licensure.[369] The numbers also indicate that the average length for which these companies estimate to be able to exclude biosimilar competitors is 40 years, with actual periods varying between 31 and 48 years.[370] The higher end of these estimates significantly outlasts the 20 years of patent protection and 12 of regulatory exclusivity contemplated in the patent and FDA statutes.[371]

The problems triggered by pay-for-delay today thus exceed the domain of a single branch of law. Because they raise anticompetitive concerns, they can be configured as core antitrust problems.[372] But that does not mean that antitrust law and antitrust regulators are the sole entities capable of addressing behaviors that unduly distort markets for pharmaceuticals.[373] FDA law and patent law are intertwined with antitrust law in the biopharmaceutical arena.[374] Monitoring pay-for-delay deals involving biosimilars should not be an activity restricted to the FTC. The string of settlements surrounding biosimilars to Humira suggests that *Actavis*' deterrent power is, in some circumstances, limited. Against this backdrop, the public interest would be furthered if additional agencies could add to the FTC's patrolling functions.

The Article thus argues in favor of cumulative *ex post* interventions from different agencies, and proceeds to illustrate how one such intervention *could* and *should* take place. It focuses primarily on the FDA as the gatekeeper of market entrance for biopharmaceutical products. It proposes a regime of license revocation for manufacturers who deliberately fail to bring their biosimilars to market after FDA approval. Such a solution eliminates the most troublesome effects of the extended lag between anticompetitive settlements and antitrust litigation and, in so doing, triages the marketplace for biosimilar competition.

B. FDA AS A LOCUS FOR ADDRESSING COMPETITION ISSUES

---

[368] See James Bessen, *Patent Thickets: Strategic Patenting of Complex Technologies* , SSRN (2003), at 1 (describing the emergence of patent thickets), available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=327760.

[369] See *infra*, note 242, at 2.

[370] *Id., ib*.

[371] The two terms are unlikely to occur in linear succession, and the actual patent term itself is often shorter for biopharmaceuticals. See Erika Lietzan & Kristina M.L. Acri, *Distorted Drug Patents*, __ WASH. L. REV __ (forthcoming 2020) (showing that, even after patent term restoration, the effective life of patents covering pharmaceuticals is often shorter than 14 years).

[372] Herbert Hovenkamp, *Antitrust and Innovation: Where We Are and Where We Should Be Going*, 3 ANTITRUST L. J. 749, 749 (2011) (noting that primary purpose of antitrust law is to promote competition).

[373] See e.g. Lina Khan, *The New Brandeis Movement: America's Antimonopoly Debate*, J. EUR. COMPETITION L. & PRAC. 131, 131-132 (2018) (noting that antitrust laws and regulators constitute only one tool in the American anti-monopoly legal and institutional framework).

[374] Carrier and Minniti, *supra* note 12. See also Jordan Paradise, *Regulatory Silence at the FDA: Impact on Access and Innovation*, 102 MINN. L. REV 2383, 2384 (fleshing out the relationship between the FDA's regulatory activity and patent law).

Our collective understanding of the FDA changed considerably in the early twenty-first century, as work by Rebecca Eisenberg[375] and other scholars [376] progressively shed light on the nuances of the role(s) played by the Agency as a regulator of pharmaceutical products. No longer regarded purely as a gatekeeper for safe and effective drugs, the FDA is now understood as a major catalyst for the production of information about the products it regulates.[377] As Amy Kapczynski has put it, the "core function" of the Agency in this field is to generate and validate "high-quality information about medicines."[378]

One aspect of the Agency's programmatic design that remains underexplored is the position of the FDA as a distorter of competition. The ways in which FDA's actions affect competition have been primarily associated with the incentives package embedded in FDA law that is available to biopharmaceutical innovators and worthy follow-on innovators. The bulk of these incentives consists of market exclusivities that vary according to the FDA-approved product[379] and that translate into delays or prohibitions on the approval of competitor products for a certain period of time.[380] More recently, the FDA has been directed to award priority review vouchers following the approval of drugs targeting selected diseases,[381] as a way to incentivize R&D in traditionally underfunded areas.[382]

The consequences of these incentives administered by the FDA bear a direct impact on competition outcomes. Most notably, the exclusivity regime gives drug manufacturers the ability to enter the market as monopoly-like players, even in the absence of patent protection. At a different level, priority vouchers shorten the timeline for regulatory review, thus allowing the bearer to enter the market earlier than under standard review.

Even though the FDA yields significant competition-distorting power, so far the Agency has not been regarded as a potential corrective locus when malfunctions arise in the context of biopharmaceutical competition. Yet, it is worth considering the FDA as an institutional player with the capability to address certain anticompetitive behaviors. The Agency is well positioned to curb

---

[375] See Eisenberg, *The Role of the FDA in Innovation Policy*, *supra*, note 54.

[376] See Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 102 MINN. L. REV. 2357 (2018). See also generally DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010) (Desc). Peter Barton Hutt et al., Food and Drug Law: Cases and Materials, 4th ed.

[377] Eisenberg, *supra*, note 54, at 347 (framing this "structural role" of the FDA as one of "promoting a valuable form of pharmaceutical innovation—the development of credible information about the effects of drugs"); Kapczynski, *supra*, note **Error! Bookmark not defined.**, at 2358-59; Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1130 (2019) (noting that the FDA "is institutionally well-positioned to serve as an information intermediary."). See also Lewis Grossman, *FDA and the Rise of the Empowered Consumer*, 66 ADMIN. L. REV. 627 (2014) (tracing the historical decline of the paternalistic view of the FDA's gatekeeping function).

[378] Kapczynski, *supra*, note **Error! Bookmark not defined.**, at 2358, 2359.

[379] See 21 C.F.R. 314.108, 316.31, 316.34; see also sections 505A, 505E, 505(j)(5)(B)(iv) and section 505(j)(5)(B)(v) of the FDCA. See also U.S. FOOD & DRUG ADMIN., *Frequently Asked Questions on Patents and Exclusivity* (2018).

[380] *Id., ib.*

[381] See David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313 (2006) (first proposing an FDA-administered voucher system).

[382] For an overview and evaluation of the voucher program, see Ana Santos Rutschman, *The Priority Review Voucher Program at the FDA: From Neglected Tropical Diseases to the 21st Century Cures Act*, 26 ANNALS HEALTH L. 71 (2017).

excesses that distort competition, as a counterpart to its own power to distort competition through the grant of exclusivities and vouchers.

The solution developed in the following section—license revocation—can be seen, among other features, as a punitive gesture directly aimed at curtailing anticompetitive behaviors like the ones embodied by pay-for-delay agreements. But it can also be seen as a corollary of the FDA's gatekeeping function. The regulator that controls access to the market also exerts the faculty of restraining previously granted market access, if an approved product fails to meet statutory or regulatory standards while being commercialized. As such, the figure of revocation would not be extraneous to FDA practice, nor to its mandate as an administrative agency. Moreover, if the FDA were to play a more overt role in competition policy than it does today, with the purpose of disincentivizing behaviors like for pay-for-delay, this would be consistent with its public health-oriented mission.[383]

As far as biosimilars are concerned, the FDA itself has self-diagnosed the misalignment between FDA approval and market entrance.[384] In mid-2018, the FDA Commissioner noted that, even though Agency had approved a total of nine biosimilars, only three were commercially available.[385] As then-Commissioner Gottlieb put it, "[i]n some cases, patent thickets on biologics deter market entry for years after FDA approval."[386]

Pay-for-delay agreements between biologic and biosimilar manufacturers stem from a misarticulation of the leading regulatory regimes governing biopharmaceutical innovation—the patent system and the FDA regulatory regime, with antitrust scrutiny lagging in time. That a dysfunctional embodiment of the innovation ecosystem should allow grantees of FDA licenses to avoid commercialization through non-use is a perversion of the regulatory regime. In this context, FDA inaction in the face of non-practicing licensees amounts to a furtherance of an undesirable distortion to competition.

The different functions performed by the FDA cannot be meaningfully isolated. While acting as an agency tasked with assessing and monitoring the safety and efficacy of pharmaceutical products, the FDA is also acting as a catalyst for the production of valuable information, a promoter of public health and, often, a distorter of competition that grants market access to one manufacturer while delaying it for others. The competition-distorting role of the FDA in biopharmaceutical markets is not necessarily a negative thing.[387] It is, first and foremost, a design feature. But this Article posits that, when certain disfunctions occur—namely, pay-for-delay—this feature should be balanced by a corrective gesture from the Agency, one that is already built into its regulatory framework.[388] The FDA has long been given statutory power to revoke licenses.[389] The final

---

[383] See U.S. FOOD & DRUG ADMIN., *What We Do* (2018) (listing the ways in which the Agency pursues public health goals).

[384] U.S. FOOD & DRUG ADMIN., *Advancing Patient Care Through Competition—Speech by Scott Gottlieb* (Apr. 19, 2018).

[385] *Id., ib.*

[386] *Id., ib.*

[387] Although some commentators have questioned whether lengthy exclusivity periods and priority vouchers really serve the purpose of promoting biopharmaceutical innovation. See e.g. U.S. GOV'T ACCOUNTABILITY OFF., GAO-16-319, RARE DISEASES: TOO EARLY TO GAUGE EFFECTIVENESS OF FDA PEDIATRIC VOUCHER PROGRAM (Mar. 2, 2016), http://www.gao.gov/products/GAO-16-319 (last accessed Jan. 9, 2020).

[388] *Infra*, Part IV.C.3 (outlining the regulatory framework for the revocation of FDA biologics licenses).

[389] See 21 C.F.R. § 601.5 (2018).

section of this Article argues that the FDA *can* use that power to revoke licenses granted to biosimilar manufacturers who fail to bring their products to market because of a pay-for-delay agreement. Moreover, the FDA *should* revoke biosimilar licenses in cases of pay-for-delay, because it is the best-placed institutional player in this field, as the PTO has limited power to break patent thickets and FTC scrutiny offers a direct but protracted response to anticompetitive behavior in the pharmaceutical arena.

C. Overview of the Proposed Framework

This section proposes an *ex post* intervention aimed at curbing pay-for-delay in the context of biologic-biosimilar competition. Specifically, it argues that the FDA should use its power to revoke biosimilar licenses in cases of unjustified inaction by biosimilar manufacturers. Such an intervention, designed to occur on a faster timeline than antitrust scrutiny, functions as a deterrent for anticompetitive behaviors and creates a signaling mechanism that clears the field for legitimate competitors to emerge.

1. The Proposed Intervention

In its gatekeeping function, the FDA has the ability to grant licenses to market certain pharmaceutical drugs. As a general principle of FDA law, manufacturers of new pharmaceutical drugs, as well as follow-on innovators,[390] are barred from bringing unapproved drugs to market, absent a permissive gesture from the FDA.[391] The ability to grant licenses is matched by the Agency's ability to revoke licenses, if certain behaviors—or lack thereof—occur.[392]

As seen above, certain licenses granted by the FDA cause significant market distortions.[393] This is the case of licenses to market biological products, particularly when a biologic is the first of its kind to receive FDA approval and a statutory exclusivity prevents competitors from entering the market for a period of 12 years, independently of the status of patent protection.

So far, the FDA has been engaging in license revocation primarily while exercising its gatekeeping role[394] in pursuit of its mission of protecting the public health,[395] but it has not done so in connection with its role in distorting competition. This Article argues that the Agency can and should revoke licenses granted to biosimilar manufacturers when they fail to bring their products to market within a certain period of time,[396] and absent a reasonable justification for the delay, defined to mean circumstances that roughly align with the concepts of impracticability, impossibility or force majeure.[397]

---

[390] An expression that encompasses manufacturers of generics drugs and of biosimilars alike.

[391] 21 U.S.C. § 355(a)(b) (prohibiting the introduction of new drugs into interstate commerce unless the FDA approves an application); 21 U.S.C. § 355(a)(j) (subjecting generic drugs to a similar prohibition and to the approval of an abbreviated application). See also *Id.* § 355(a) (framing the prohibition as one of "introduce or deliver for introduction into interstate commerce").

[392] 21 C.F.R. § 601.5.

[393] *Supra*, Part IV.B.

[394] And, indirectly, as per its information-producing role.

[395] U.S. Food & Drug Admin., What We Do, https://www.fda.gov/about-fda/what-we-do (last accessed Jan. 9, 2020).

[396] 21 C.F.R. § 601.5(2).

[397] *Infra*, Part IV.C.2.

As developed below, this proposal seeks to accomplish four goals. First, it provides a direct fix for a gamesmanship problem within overlapping regulatory regimes.[398] Second, it seeks to mitigate the consequences[399] of a problem that originates elsewhere in the administrative state, as dozens or hundreds of patents are awarded to a single biologic, enabling tiered litigation strategies.[400] Third, it creates a signaling feature, as biosimilar manufacturers seeking FDA approval indicate that they are prepared to either see patent litigation through, or avoid existing patents altogether—as entering into a settlement with the manufacturer of the reference biologic will translate into losing their license.[401] And fourth, it restores meaning to the licensing activity of the FDA, which has been stripped of its intended function as two-thirds of the first nine biosimilars approved by the Agency have not entered the market.[402]

The proposal is confined to cases of pay-for-delay involving biosimilars, given the particular characteristics of competition in this field, as well as the costs to patients and health systems affected by the unavailability of biosimilar alternatives in the United States market. It is not proposed in lieu of antitrust scrutiny, but rather as a checkpoint for a specific type of anticompetitive behavior located outside the core antitrust avenues for patrolling heterogenous anticompetitive behaviors. And, finally, the proposal does not address the larger problems of regulatory design and interagency coordination of which pharmaceutical pay-for-delay agreements take advantage, but provides a localized fix designed to diminish the frequency and impact of these agreements.

2. Mechanics and Implementation of the Proposal

If subjected to the possibility of license revocation, manufacturers of biosimilars receiving approval from the FDA would have a certain period of time to start manufacturing their products and to bring them to market. Past that period, and absent a reasonable justification, the FDA would take steps to revoke the biosimilar license.

FDA approval normally marks the last regulatory hurdle to commercialization of products subject to pre-market review. Because of the distortions to the post-approval timeline that are now pervasive in the case of biosimilars, this proposal advocates for the determination of a reasonable period of time for the license grantee to bring the biosimilar to market.[403] The semi-formalized qualification comes from the fact that this period of time should be established by FDA guidance,

---

[398] See Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685, 687 (2009) (defining regulatory gaming as "private behavior that harnesses procompetitive or neutral regulations and uses them for exclusionary purposes").

[399] See Tejas N. Narechania, *Patent Conflicts*, GEO. L. J. 1483, 1485-1486 (2015) (listing instances of direct and indirect action by non-patent agencies, including the Federal Trade Commission and the National Institutes of Health, in cases involving patent conflicts); see also W. Nicholson Price II & Arti K. Rai, *How Logically Impossible Patents Block Biosimilars*, 37 NATURE BIOTECH. 862 (2019).

[400] *Supra*, Part III.A.2.

[401] *Infra*, Part IV.C.3.

[402] See *supra* note 202; see also Appendix 2.

[403] This idea is consistent with existing regulations, which contemplate a "reasonable" period during which the manufacturer of a biologic can "demonstrate or achieve compliance" before license revocation. 21 C.F.R. § 601.5(b)(2) (2018). See also *infra*, Part IV.C.3.

an "informal tool"[404] widely used by administrative agencies. The FDA, like other federal regulatory agencies, uses guidance "to set policy broadly and prospectively" instead of resorting to formal rulemaking processes.[405] In the case of biosimilar licenses, issuing guidance would be the most flexible and least cumbersome way for the Agency to communicate with industry, affording interested parties and the public in general the possibility of commenting on draft versions.[406] Moreover, and if appropriate, the malleability of guidance would allow the FDA to set different timelines and specifications for different types of biosimilars, as well as to move from general timeline parameters to more precise formulations (and vice-versa) as needed.

This Article is agnostic as to the specific duration of this period of time. Such a determination is best left to the regulator with expertise in the field. The relevant element is that the establishment of a non-arbitrary deadline for commercialization of an approved biosimilar clearly conveys the expectations of the Agency to manufacturers. At the same time, it keeps the FDA involved in the indirect monitoring of competition outcomes: if the clock runs out and no reasonable justification is provided, then the Agency would revoke the biosimilar license.

Revocation would occur according to the general administrative rules governing FDA actions, which are further detailed in the following sub-section. It would be nonetheless possible for a biosimilar manufacturer to show evidence that a delay is attributable to exogenous circumstances and therefore obtain a revised deadline from the Agency.[407] The FDA has the ability to develop a framework contemplating "reasonable delays" through guidance. Because the manufacturing of biological products is significantly more complex than the manufacturing of conventional drugs,[408] a natural fit for this category would be unforeseen issues affecting the manufacturing process. Additionally, guidance could contemplate other factors, ranging from production delays attributable to third-party actions to force majeure events. Absent a reasonable justification for the delay, the FDA would proceed to revoke the license.

There are different possible embodiments of this proposal. In its simplest form, revocation would be a stand-alone measure. The following sub-section makes the case that the FDA currently has the authority to revoke biosimilar licenses based on the manufacturer's failure to bring the licensed product to market.[409] In more stringent versions of the proposal, which would require regulatory or legislative intervention—and which therefore would be more challenging[410] to implement—revocation could be coupled with a time ban on reapplying for a license, or restrictions on data resubmission.

---

[404] Tim Wu, *Agency Threats*, 60 DUKE L. J. 1 (2010); see also Nina A. Mendelson, *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L REV. 397, 398 (2007) (noting that the amount of guidance issued by federal regulatory agencies is "massive").

[405] Mendelson, *id.*, at 397.

[406] U.S. FOOD & DRUG ADMIN., *Guide to Submitting Comments to the FDA* (2018).

[407] This is consistent with longstanding regulations governing revocation of licenses for biologic products. These regulations require, inter alia, a "reasonable" notification period during which the manufacturer can "demonstrate or achieve compliance' with regulatory requirements before the FDA institutes revocation proceedings. 21 C.F.R. § 601.5(b)(2) (2018). See also *infra*, Part IV.C.3.

[408] Price II & Arti K. Rai, *Manufacturing Barriers*, *supra* note XX, at 1033-1036 (highlighting path-dependency and unexpected physiological effects arising in connection with the manufacturing process).

[409] This authority is grounded on regulatory language; see 21 C.F.R. § 601.5(1)(a)(ii).

[410] *Infra*, Part IV.C.5.

3. The Possibility of License Revocation by the FDA

As an administrative agency, the FDA is subject to general administrative principles and rules. The Administrative Procedure Act (APA) gives agencies the ability to grant different types of licenses, which are collectively defined as including "the whole or a part of an agency permit, certificate, approval, registration, charter, membership, statutory exemption or other form of permission."[411] The APA also contemplates several measures that can be taken by administrative agencies to penalize license holders for certain behaviors.[412] These measures range from the imposition of economic sanctions such as fines[413] to the invalidation of previously granted licenses.[414]

The FDA is also subject to a specific regulatory framework governing the revocation of licenses. Title 21 of the Code of Federal Regulations, which sets forth the general regulatory framework for FDA-regulated products, addresses the possibility of license revocation in connection with different scenarios.[415] These depend on the product at stake, as well as on the underlying causes of revocation.

With regard to biologics, the circumstances under which the FDA may revoke a license fall broadly into four categories.[416] First, license revocation may occur in cases in which the Agency is notified of a manufacturer's intention to discontinue the manufacture of all or some of the products covered by a license.[417] Second, the FDA has the authority[418] to take steps to revoke a license when certain behaviors from the manufacturer effectively undermine the Agency's ability to carry out inspections or to monitor changes affecting licensed products.[419] Third, the Agency has the authority to revoke a license in connection with material violations of licensing standards, a category that includes significant changes involving a licensed product, methods of manufacturing or the manufacturing establishment, as well as notification failures. [420] Lastly, license revocation may also occur when the licensed product can no longer be considered safe or efficacious, or is deemed misbranded.[421]

---

[411] 5 U.S.C. § 551(1)(8); see also *id.* § 551(1)(9) (defining licensing as including "agency process respecting the grant, renewal, denial, revocation, suspension, annulment, withdrawal, limitation, amendment, modification, or conditioning of a license").

[412] 5 U.S.C. § 558 (generally subjecting these measures to jurisdictional and procedural limitations).

[413] Id. and 5 U.S.C. § 551(10) (listing the types of sanctions susceptible of being imposed by administrative agencies).

[414] 5 U.S.C. § 558(c).

[415] 21 C.F.R. § 601.5 (2018). See also 21 U.S.C. § 371 and 21 C.F.R. § 10 (2018) (delineating the general framework for the Agency's administrative practices and procedures).

[416] Id. C.F.R. § 601.5 (2018).

[417] Id. C.F.R. § 601.5(a) (2018).

[418] Id. C.F.R. § 601.5(b)(1) (2018) (framing revocation as a mandatory under certain circumstances: "The Commissioner *shall* notify the licensed manufacturer of the intention to revoke the biologics license (…) *if the Commissioner finds* any of the following (…)" [italics added]).

[419] Id. C.F.R. § 601.5(b)(1)(i-ii) (2018).

[420] Id. C.F.R. § 601.5(b)(1)(iii-iv) (2018).

[421] Id. C.F.R. § 601.5(b)(1)(v-vi) (2018) (this category includes cases in which changes affecting the licensed product are so substantial that a new regulatory review is needed).

The regulations further establish the procedural framework for revocation of FDA licenses, which impose several obligations on the Agency, from notification and hearing requirements[422] to the concession of a "reasonable period" for manufacturers to demonstrate compliance or bring their practices into compliance.[423]

In cases of pay-for-delay, licensure is followed by prolonged inaction on the part of the biosimilar manufacturer. From an administrative policy perspective, this behavior is undesirable, as it frustrates the purpose for which the license was granted while displacing resources within an agency. In the case of the FDA, the failure to bring an approved biosimilar to market additionally weakens the catalyzing role of the Agency in the production of information. A normal licensure procedure culminates in the commercialization of a biopharmaceutical drug, maintaining the flow of data production as the drug is monitored throughout the post-market stage through surveillance studies and reporting requirements. Under pay-for-delay, that flow is broken. The permission granted by the FDA is not reciprocated by continued production of data, but rather followed by stagnating levels of information about the approved product. Adding to this problem, the outcome of the licensure process is at odds with the time and resources allocated by the FDA during the review process: the FDA grants a permission that is not acted upon. For an agency that has recently made some important strides in diminishing application backlog, and which can easily be affected by external constraints,[424] the mismatch between the resource allocation and frustrated market entrance is not insignificant.

The language of the revocation provisions in the Code of Federal Regulations can be used to support the view that the FDA can revoke a license due to inaction on the part of the biosimilar manufacturer, coupled with the ensuing lack of information generated about an FDA-approved product. § 601.5(b)(1)(ii) authorizes the FDA to initiate proceedings to revoke a biologics license when "[m]anufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made." This provision is one of several in which license revocation constitutes a remedy to manufacturing insufficiencies. § 601.5(b)(1)(ii) specifically addresses cases in which manufacturing activity has been reduced to inordinately low levels, which consequently and similarly decreases the production of information about the licensed product. The unusual and quasi-oxymoronic word choice—"discontinued to an extent"—seems to indicate that the law is contemplating situations in which manufacturing outputs are virtually zero. Discontinued production is a different concept from very low levels of production,[425] but the language appears to imply the admissibility of a range of discontinuation—or, more properly, of reduced levels of production—for which license revocation becomes the remedy if production does not rise to meaningful levels.[426] As such, the language indicates that the primary concern of the regulator is to avoid situations in which manufacturing for the United States market of an FDA-approved biologic falls to zero, or to levels that are materially equivalent to zero.

---

[422] Id. C.F.R. § 601.5(b)(1) (2018).

[423] Id. C.F.R. § 601.2 (2018).

[424] See e.g. Alexander Gaffney, *Post-Shutdown, FDA Faces Backlog of Work*, PWC (Feb. 1, 2019) (noting the impact of the 2019 government shutdown on the Agency's review timeline).

[425] Common definitions of "discontinued" equate it with "to break continuity," "cease to operate, administer, use, produce, or take," "abandon or terminate." Merriam-Webster (2019).

[426] Cfr. 21 C.F.R. § 601.5(b)(2) (giving manufacturers a "reasonable period" to "demonstrate or achieve compliance").

The framing provision in § 601.5(b)(1), to which the discontinuation provision is subject, states that the Agency "*shall* notify the licensed manufacturer of the intention to revoke the biologics license." The enabling language in this section is thus mandatory. Not only *can* the FDA revoke licenses in situations within the purview of § 601.5(b)(1)(ii), it *should* do so.

The articulation of these two provisions provides a framework through which the Agency addresses situations of inexistent or quasi-inexistent manufacturing levels. If the regulator mandates license revocation in cases in which manufacturing levels are close to "discontinuation," then the revocation framework has to contemplate cases in which manufacturing levels are zero or have never risen above zero. A logical interpretive principle of *a maiore ad minus* should apply here: if the law has a punitive gesture towards levels of productions that are materially equivalent to zero, then it must also encompass situations in which manufacturing levels have never been greater that zero. What happens in situations of pay-for-delay falls squarely under this framework: inaction at the manufacturing level, with consequent unavailability of the FDA-approved product in the market, in disregard of the licensure process.

A contextual analysis further enhances this reading. The interpretation of the regulations offered above is consistent with the spirit of § 601.5(a), which mandates license revocation ("[a] biologics license *shall* be revoked") whenever the manufacturer of an approved biologic notifies the FDA of its intention to discontinue production of an approved product.[427] If a manufacturer chooses (or is forced) to bring levels of production down to zero, the justification for the maintenance of the license ceases to exist.

In addition to establishing the framework for license revocation, it is worth noting that § 601.5 also contains a balancing mechanism, giving manufacturers the opportunity to bring production levels to a meaningful threshold within a "reasonable period" of time.[428] The proposal outlined in the previous section of this Article put forward an explicit embodiment of this requirement,[429] developed through guidance.[430]

The FDA should thus revoke the licenses of biosimilar manufacturers engaging in pay-for-delay after a reasonable period of time. If applied properly, the existing regulatory framework should have resulted in the revocation of the licenses of Humira competitors who gained FDA approval but failed to manufacture the approved biosimilar,[431] or in a nudge towards compliance with manufacturing requirements.[432]

4. Advantages of the Proposal

In addition to applying the existing legal framework for license revocation in a manner that is consistent with linguistic and teleological interpretive principles, the proposal outlined above serves several other goals.

---

[427] Id. § 601.5(a) (2018).

[428] Id. § 601.5(b)(2).

[429] But see *i.d.* § 601.5(b)(2) and § 601.6(a) (establishing that the "reasonable period" period requirement ceases to apply in cases in which the Agency reasonably believes that the public health is being harmed); *id.* § 601.5(b)(2) (doing the same "in cases involving willfulness").

[430] *Supra*, Part IV.C.2.

[431] The existence of a pay-for-delay agreement should constitute prima facie evidence of violation of the conduct required by 21 C.F.R. § 601.5(b)(ii) and § 601.5(b)(2).

[432] Part IV.C.5 further explores the advantages of license removal as a nudge mechanism.

First, it constitutes an indirect but more timely response to anticompetitive behaviors than the one normally provided by institutions that directly monitor antitrust issues. Consider, for instance, the case of Amgen, the first biosimilar company to settle with AbbVie.[433] The FDA approved Amgen's biosimilar in September 2016, just over three months before the expiration of Humira's composition patent.[434] The pay-for-delay settlement took place in September 2017.[435] As of early 2020, Amgen's license is still valid, even though no manufacturing for the United States market has occurred. Now imagine that the reasonable period granted by the FDA was one year, counted from January 1, 2017.[436] Assuming no significant hurdles to manufacturing during that period,[437] license revocation would have occurred in early 2018. Even if, for the sake of the argument, the reasonable period were fixed at two years, revocation would occur in early 2019, months before the beginning of the antitrust response. Even though these dates are artificial, they illustrate the ability of the FDA to address, albeit indirectly, a competition-related problem. License revocation is a nimbler tool than direct antitrust responses to pay-for-delay.

The second advantage of the solution proposed in this Article is its signaling function. Were the FDA to apply the existing revocation framework to pay-for-delay, a biosimilar company seeking regulatory approval would be signaling to competitors its intention to see the licensure process through. This signal would be especially meaningful in the case of patent challenges, as it would indicate confidence in the probability of success of the challenge. Moreover, in versions of the proposal encompassing additional measures—such as a temporal ban on reapplication for a license—the signaling function would be even stronger.

As the following sub-section acknowledges, license revocation may have a chilling effect on the number of biosimilar manufacturers seeking FDA approval, particularly when several secondary patents on a biologic are valid or have yet to be invalidated. But the third effect of the proposal is that it may nudge some biosimilar manufacturers to channel resources towards challenging weak patents in the biopharmaceutical space. While the overall number of biosimilar manufacturers seeking market entrance may be smaller under the threat of license revocation, the number of follow-on competitors needed on the market for prices to drop is actually fairly small.[438] As further detailed below, market saturation happens quickly in this field,[439] and therefore even if the overall number of potential market entrants is lower under the proposed framework, the number of manufacturers who need to be able to navigate R&D, regulatory review and potential patent litigation, remains very low. At the same time, the economic return available for those few who succeed in entering the market is not negligible. As such, even if the proposal may lead to a certain degree of R&D attrition, the economic incentive to come to market is not displaced. License revocation eliminates pay-for-delay and clears the field for highly motivated players to seek product commercialization, potentially even sooner than under current practices.

Finally, another angle of this proposal is that it restores meaning to the licensing activity of the FDA. By leaving manufacturing inaction unpenalized in the short term, an empty space at the intersection of different branches of the law allows companies to seek and obtain FDA approval

---

[433] See Appendix 2.

[434] *Id.*

[435] *Id.*

[436] The first day after the expiration of the composition patent on Humira, for the sake of simplicity.

[437] As there have not been any in the manufacturing of the biosimilar for the European market.

[438] See Davio, *Momenta Drops Biosimilar Adalimumab from Pipeline*, *supra* note 40 and accompanying text.

[439] *Infra*, Part IV.C 5.

without any intention of entering the market for years.[440] As such, FDA licensure is reduced to empty gesture. For an agency that is now staunchly embedded in biopharmaceutical innovation policy, this is especially problematic.

5. Drawbacks of the Proposal

A feature of this proposal is that it specifically targets only one of the parties engaging in anticompetitive behavior. If implemented, were a Humira-type deal to occur, AbbVie would not be directly affected by the intervention of the FDA, whereas Amgen and any other biosimilar companies entering into pay-for-delay agreements would. In stronger versions of the proposal, there is a punitive element added to license revocation—for instance, in the form of a temporal ban on seeking regulatory approval—that further renders the proposal harsher towards follow-on competitors.

Nevertheless, it is worth pointing out that even stronger versions of the proposal target biosimilar manufacturers only *if* and *because* their status switches from would-be competitors to gamers of the regulatory system. While a symmetrical framework would be formally fairer in absolute terms, it would be impracticable from the perspective of co-involving the FDA in addressing pay-for-delay. License revocation grounded in manufacturer inaction does not apply to the first-comer to market, but to follow-on innovators who fail to compete. AbbVie's behavior is problematic from different angles, chief among which antitrust law, but not in terms of meeting the manufacturing requirements that attach to the grant of an FDA license. Beyond this technical aspect, as a matter of policy, the goal of the proposal is to bring follow-on products to market sooner, not to diminish the influx of life-changing and life-savings drugs to market. Moreover, and as a balancing mechanism, the party not targeted by the FDA intervention under the proposed framework is not exempted from legal scrutiny: it merely happens at a different time and through the lens of a different branch of the law.

A different type of objection to the proposal relates to the political economy. As Daniel Carpenter has recently observed, the FDA operates within "an inescapable political world."[441] In terms of implementation, the previous sub-section delineated a pathway for application of the existing license revocation framework to pay-for-delay. In its most straightforward form, the proposal does not require legislative intervention and is entirely FDA-administered. But legislative action would likely be required to adopt more expansive forms of the proposal. Given the fact that topics related to biopharmaceuticals are at the center of some of the most politically charged debates in the United States, this is not a trivial drawback. While this issue does not present itself solely in connection with this proposal, it certainly decreases the likelihood that stronger versions of the proposal will be adopted. Nevertheless, it is worth noting that currently there are efforts across the political spectrum supporting a variety of measures aimed at lowering the price of prescription drugs.[442] As a tool to bring biosimilars to market faster, even stronger versions of the

---

[440] *Supra*, Part III (describing licensure of biosimilars to Humira in cases in which the sponsor of the biosimilar had previously entered into an anticompetitive agreement with Humira's manufacturer).

[441] Daniel Carpenter, *FDA Transparency in an Inescapable Political World*, 45 J. L. MED. & ETHICS 29 (2017).

[442] See e.g. Susan Cornwell & Michael Erman, *Senators Announce Bipartisan Proposal to Lower Drug Prices*, REUTERS (Jul. 23, 2019); Michael Erman & Carl O'Donnell, *White House Preparing Order That Would Cut Drug Prices for Medicare*, REUTERS (Jul. 24, 2019); Susan Cornwell, *U.S. Speaker Pelosi Unveils Drug Price Plan, Trump Welcomes It*, REUTERS (Sept. 19, 2019). It is also worth noting that the FTC supports legislation to curb pay-for-delay. See U.S. FED. TRADE COMM'N, PAY-FOR-DELAY: WHEN DRUG COMPANIES AGREE NOT TO COMPETE, https://www.ftc.gov/news-events/media-resources/mergers-competition/pay-delay.

license revocation proposal are consistent with these goals, despite the need for changes to the law and regulations.

Another dimension of the political economy is that the FDA derives a substantial amount of its funding from industry. In fiscal year 2018, for example, the overall budget of the Agency was $5.4 billion, of which 55% ($3 billion) derived from federal budget authorization and 45% ($2.4 billion) came from industry user fees.[443] While being mindful of this feature and of the fact that the FDA interacts constantly with industry,[444] the proposal does not fundamentally upend the FDA-industry relationship. Instead, its core advocates for the application of existing law. As a by-product, a relatively small number of firms would be affected by license revocation or the threat thereof.[445] From this perspective, the proposal might be more palatable to the pharmaceutical industry as a whole than at first blush. Additionally, and more importantly, disruption of the status quo should not be a valid justification for the Agency to shy away from fulfilling its role in license revocation, or for possible legislative changes to be summarily discounted.

Finally, revisiting the problem of chilling effects outlined in the previous sub-section, it is entirely possible that fewer biosimilar companies would seek regulatory approval under a system in which license revocation looms as a response to pay-for-delay. Nevertheless, given the size of the market for biologics, the incentive to become the second or third market entrant remains in place. In fact, given the costs associated with developing and manufacturing biosimilar products, one of the early lessons in the economics of biosimilar competition has been that the number of follow-on innovators able to enter the market until returns become sub-competitive is small. Once again, the case of Humira illustrates this point: between September 2017 and May 2019, nine biosimilar companies entered into pay-for-delay agreements with AbbVie;[446] in August 2019, Momenta, a company that was developing a biosimilar to Humira, announced that it would stop R&D on the project and reallocate around $100 million to the development of a different biosimilar.[447] The company explicitly credited market saturation in the Humira biosimilar space as one of the main reasons for the switch.[448] Against this backdrop, while the proposed FDA intervention would diminish competition from a quantitative perspective, the possibility of tapping into multi-million dollar revenue streams should be sufficient to preserve enough economic incentives for a limited number of follow-on firms to seek market entrance.

Throughout its evolution as a public-health oriented agency, the FDA has acquired innovation-promoting and competition-distorting power, while retaining its mission of promoting and maintaining the public health. A solution that preserves the goal of bringing motivated biosimilar manufacturers to come to market—and, as a consequence, the indirect goal of lowering prices of the most promising and expensive drugs available to patients—is ultimately consistent with these goals.

---

[443] U.S. FOOD & DRUG ADMIN., FDA AT A GLANCE (2018).

[444] Robert M. Califf, *Transparency at the U.S. Food and Drug Administration*, 45 J. L. MED. & ETHICS 24, 24-25 (2017).

[445] One of the consequences of the asymmetrical nature of the proposal is that there would also be less disruption of the status quo for big pharma than under other proposals targeting anticompetitive behaviors or high drug of prescription drugs.

[446] See Appendix 2.

[447] See *supra* note 438 and accompanying text.

[448] See GABI, *Momenta Drops Humira Biosimilar Development* (Aug. 30, 2019).

CONCLUSION

As the world's most expensive—and most needed—drugs begin losing patent protection in the United States, one would expect cheaper versions of these drugs to become available to patients. Yet, as seen above, that has not been the case, even when fully developed biosimilars have received FDA market approval.

In addition to the behavior of private firms, exemplified above by the Humira case study, several imbalances rooted in seemingly unrelated parts of the administrative state contribute to this scenario. From the likely excessive number of patents issued by the PTO covering a single drug to the temporal lag problem inherent to antitrust scrutiny, it has been relatively easy for anticompetitive behaviors to proliferate and remain unchecked for extended periods of time, with potentially devastating consequences to the health of patients and at onerous costs to health systems.

This Article has identified a new institutional locus for more timely interventions seeking to address these types of anticompetitive behaviors. As a pre-market gatekeeper with post-market monitoring functions, as well as in its role as a catalyst for the production of information, the FDA is well positioned to both penalize and disincentivize gamesmanship of the regulatory system in the area of biologic-biosimilar competition, while clearing the pathway for motivated players to bring cheaper drugs to market. The Article has further argued that the proposed solution—license revocation—is already supported by existing regulatory language, even if not by agency practice. Alternative embodiments of a license revocation-based scheme are also possible, including interventions by regulators or legislators that would direct the Agency to start applying the existing revocation provisions to ongoing cases.

Finally, and beyond features which are specific to the field of biopharmaceutical products, the Article has sought to call attention to a less-explored dimension of FDA activity: in addition to its canonical functions, the FDA should also be understood as a distorter of competition, as illustrated by the multiple market exclusivity regimes it operates and its priority voucher program. When considered in this light, the Agency should not be discounted as a possible player in the search for responses to competition-driven problems—a topic with larger ramifications across legal regimes worth exploring in future scholarly dialogue.

APPENDIX 1

Humira's Patent Estate

Approved Indication	Rheumatoid Arthritis	Gastro Indications	Psoriasis	Psoriatic Arthritis	Ankylosing Spondylitis	Juvenile Idiopathic Arthritis	Hidradenitis Suppurativa
Composition of Matter	Expired Dec. 31, 2016						
Indication / Method of Treatment	**4 patents** Earliest Expiry: 2022	**6 patents** Earliest Expiry: 2022	**3 patents** Earliest Expiry: 2023	**4 patents** Earliest Expiry: 2023	**3 patents** Earliest Expiry: 2022	**1 patent** Expiry: 2030	**1 patent** Expiry: 2031
Formulation	14 Patents Expire 2022 – 2028						
Manufacturing	24 patents Expire 2027 – 2034						
Other (Device, Diagnostics, etc.)	15 patents Expire 2024 – 2032						

Table 1: Adapted from Richard Gonzalez, AbbVie Long-Term Strategy, ABBVIE (Oct. 30, 2015)

APPENDIX 2

Chronology of Settlements between AbbVie and Biosimilar Companies

Biosimilar Company	Settlement Date	Agreed Entry Date (U.S.)	Biosimilar FDA Approval
Amgen	9/ 28/2017	1/31/2023	9/23/2016
Samsung Bioepis	4/5/2018	6/30/2023	7/23/2019
Mylan	7/17/2018	7/31/2023	NA
Sandoz	10/11/2018	9/30/2023	10/31/2018
Fresenius Kabi	10/17/2018	9/30/2023	NA
Momenta	11/6/2018	11/20/2023	NA
Pfizer	11/30/2018	11/20/2023	NA
Coherus	1/25/2019	12/15/2023	NA
Boehringer Ingelheim	5/14/2019	7/1/2023	8/25/2017

Table 2: Adapted from Zachary Brennan, Six Lawsuits Target AbbVie's Humira and its Patent Thicket, RAPS (Apr. 2, 2019)