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## The Uncharted Waters of Competition and Innovation in Biological Medicines

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# THE UNCHARTED WATERS OF COMPETITION AND INNOVATION IN BIOLOGICAL MEDICINES

ERIKA LIETZAN\*

## ABSTRACT

*In 2010, Congress fundamentally changed how federal law encourages the discovery and development of certain new medicines and for the first time authorized less expensive “duplicates” of these medicines to be approved and compete in the marketplace. The medicines at issue are biological medicines—generally, medicines made from, or grown in, living systems. Many of the world’s most important and most expensive medicines for serious and life-threatening diseases are biological medicines. Today, that law is beginning to bear fruit; FDA has begun to approve the first of these duplicates, called “biosimilars,” and the products have begun to enter the marketplace.*

*We have a profound interest in understanding and evaluating the impact of this legislation on innovation and competition in medicine. Scholars and courts considering this question may be tempted to reason from, or analogize to, experience with generic drugs. The generic drug statute, which applies to ordinary drugs, most of which are small and chemically synthesized, is thirty years old. It has yielded a rich field of scholarship and jurisprudence relating to innovation and competition. The 2010 biosimilar law was similar to the 1984 generic drug statute in basic purpose and structure. But the biologic framework as a whole—the complete landscape within which innovation and competition in biological medicines take place—is profoundly different from anything that scholars and courts have seen before. We are in uncharted waters.*

*This Article is the first piece of legal scholarship to offer a high-level map to those waters, organized around the characteristics that define the biologic framework and distinguish it from the thirty-year-old conventional drug framework. It makes two claims. First, the pathway to market, the competitive landscape, and the means and extent of market penetration for biosimilars are likely to vary from product to product and maybe even from company to company. They are also likely to evolve over time. The variability and dynamic nature of the biosimilar pathway and market penetration distinguish the biologic framework from the drug framework. Second, biologic patents have been severed from the regulatory paradigm. Patents are more clearly distinguished, in purpose and function, from the primary regulatory device designed to reward preclinical and clinical research—data exclusivity. The regulatory scheme does not reinforce biologic innovator patents the way the drug regulatory scheme reinforces drug patents. And, although the biologic framework makes premarket patent litigation possible, it omits the regulatory incentives to achieving premarket resolution of patent disputes that have been a hallmark of the drug scheme for more than thirty years.*

*Although scholars and policymakers focusing on innovation and competition with respect to medicine have decades of experience with the generic drug paradigm, this experience may be mostly irrelevant when it comes to biologics. The specific differences between the two frameworks, and the broader thematic divergence at play in the biologic framework, have profound implications for analysis of the marketplace. This Article fills a needed gap, by providing a basis for understanding how fundamentally the biologics framework differs and, in the final Section, precisely how these differences may matter.*

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## I. INTRODUCTION

After a tornado lifts, spins, and drops her Kansas farm-house, Dorothy Gale steps out, holding her terrier, and steps slowly and wide-eyed through a fantastical new landscape: large, vividly colored plants, low white buildings with tiny windows and thatched roofs, and brightly dressed munchkins hiding amongst the flowers. “Toto,” she says, “I’ve a feeling we’re not in Kansas anymore.” This line from the 1939 movie adaptation of *The Wizard of Oz* has become part of our social lexicon, used to refer to new situations that are deeply unfamiliar and potentially outside our scope of understanding.<sup>1</sup> In 1984, Congress enacted a statute permitting approval of generic copies of innovative drugs. Twenty-six years later, it enacted a statute permitting licensure of biosimilar versions of innovative biological medicines, and, simply put, we’re not in Kansas anymore.<sup>2</sup>

Although the two medicine approval statutes are similar in basic design and goal, the biologic framework as a whole—the complete landscape within which innovation and competition in biological medicines will now take place—is profoundly different from anything that scholars and courts have seen before. We are, to offer another metaphor, in uncharted waters. This Article provides a map of those

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1. @JeremiahBullfrog, *We’re Not in Kansas Anymore*, URBAN DICTIONARY (Dec. 2, 2008), <http://www.urbandictionary.com/define.php?term=we%27re+not+in+kansas+anymore&defid=3518170> [<https://perma.cc/N93G-42LU>]; see *THE WIZARD OF OZ* (Metro-Goldwyn-Mayer 1939).

2. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

waters, organized around the characteristics that define and distinguish the new biologic framework from the conventional drug framework.

Understanding the defining characteristics of the biologic framework is both important and urgent. The enactment of a pathway for approval of biosimilar applications—which rely on an innovator’s research and which propose products that may infringe the innovator’s patents—effects a fundamental change in the regulatory, intellectual property, and competitive landscape for biological medicines. Society has a profound interest in monitoring the impact of this sea change on the pace, and nature, of innovation in biological medicines. We also have a profound interest in monitoring behavior in the resulting marketplace, particularly whether meaningful biosimilar competition emerges and benefits consumers, and whether firms act in manners consistent with the norms of fair competition. In short, we need to know that this radically new landscape both stimulates innovation and ensures timely and fair competition in biological medicines.

In the decades since enactment of the generic drug statute, a rich academic literature has developed regarding competition and innovation in the drug framework. Although scholars have begun work on regulatory and intellectual property issues relating to biosimilars, this is the first piece of scholarship to offer a broad vision of the new biologic framework organized around its defining characteristics.<sup>3</sup> This Article comes at a crucial time, because the Food and Drug Administration (FDA) has begun to license biosimilars.<sup>4</sup> Nearly a dozen applications were pending in the first quarter of 2016, and in the

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3. While this Article is the first of its kind, descriptive scholarship considering the legislation as a whole does exist. See Anna B. Laakmann, *The Hatch-Waxman Act’s Side Effects: Precautions for Biosimilars*, 47 LOY. L.A. L. REV. 917, 920, 941 (2014) (arguing that the unintended side effects of the generic drug scheme—such as “convoluted products liability rules” and the propagation of “patents of questionable value”—should serve as “precautionary guideposts” for implementation of the biosimilar statute); Jordan Paradise, *The Devil is in the Details: Health-Care Reform, Biosimilars, and Implementation Challenges for the Food and Drug Administration*, 51 JURIMETRICS J. 279 (2011) (providing an overview of the new statute and FDA’s implementation then to date); Matthew J. Seamon, *Antitrust and the Biopharmaceutical Industry: Lessons from Hatch-Waxman and an Early Evaluation of the Biologics Price Competition and Innovation Act of 2009*, 34 NOVA L. REV. 629 (2010) (summarizing the legislation, noting its importance to the healthcare finance system, and listing concerns about antitrust compliance in the generic drug marketplace).

4. By October 2016, FDA had licensed four biosimilars: Zarxio® (filgrastim-sndz), Inflectra® (infliximab-dyyb), Erelzi® (etanercept-szss), and Amjevita® (adalimumab-atto); these referenced Neupogen® (filgrastim), Remicade® (infliximab), Enbrel® (etanercept), and Humira® (adalimumab), respectively. See FDA, LIST OF LICENSED BIOLOGICAL PRODUCTS WITH (1) REFERENCE PRODUCT EXCLUSIVITY AND (2) BIOSIMILARITY OR INTERCHANGEABILITY EVALUATIONS TO DATE (2017), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf> [https://perma.cc/9K37-72RD].

third quarter FDA reported 66 biosimilar products in development, pertaining to 20 innovative products.<sup>5</sup> Various patent disputes relating to pending or planned biosimilar applications are underway or have concluded, at the Patent and Trademark Office (PTO) or in the federal courts.<sup>6</sup> Thus, although the scheme was perceived as slow to launch, the next few years could bring a sizeable number of biosimilar market entrants.<sup>7</sup>

Development of a rich academic discourse around innovation and competition in biological medicines will require understanding the broader framework within which that innovation and competition occur and the ways in which it differs from the familiar drug framework.

This Article claims that the biologic framework differs in two essential ways. *First*, unlike the drug framework, the biologic framework is variable and dynamic. That is, the rules and considerations relevant to biosimilar premarket licensure and market penetration may vary by product class and, perhaps, also by product and by applicant. Further, these rules and considerations are developing in parallel with licensure of the first products and are likely to evolve as the agency and industry gain comfort with the scheme and as the science matures. The framework is therefore dynamic. Scholars and courts will be considering innovation and competition within a framework that is idiosyncratic and evolving. *Second*, the biologic framework separates patents, functionally and conceptually, from the regulatory paradigm. To begin with, the primary regulatory mecha-

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5. Zachary Brennan, *FDA's Biosimilars Workload: 57 Development Programs, \$81M Spent in First Three Fiscal Years*, REG. AFFS. PROF. SOC'Y (Mar. 14, 2016), <http://raps.org/Regulatory-Focus/News/2016/03/14/24531/FDA%E2%80%99s-Biosimilars-Workload-57-Development-Programs-81M-Spent-in-First-Three-Fiscal-Years/> [https://perma.cc/8AFT-8BEJ?type=image]; Michael Mezher, *FDA Officials Share Best Practices for Biosimilar Development*, REG. AFFS. PROF. SOC'Y (Oct. 28, 2016), <http://www.raps.org/Regulatory-Focus/News/2016/10/28/26093/FDA-Officials-Share-Best-Practices-for-Biosimilar-Development/> [https://perma.cc/8XBK-6TM2].

6. *E.g.*, Amgen Inc. v. Apotex Inc., Case No. 15-61631-CIV (S.D. Fla.) (Findings of Fact and Conclusions of Law) (Sept. 6, 2016) (finding that Apotex's biosimilar applications for filgrastim and pegfilgrastim do not infringe U.S. Patent No. 8,952,138, which covers a process of protein refolding); Boehringer Ingelheim v. Genentech, Inc., No. IPR2015-00417 (P.T.A.B. July 14, 2015) (relating to U.S. Patent No. 7,976,838, which claims a method of treating rheumatoid arthritis by administering an anti-CD20 antibody, namely, rituximab) (settled).

7. The Director of FDA's Center for Drug Evaluation and Research recently warned that the agency's biosimilar program may soon "explode." Sue Sutter, *Biosimilar User Fee Agreement Offers FDA Funding Boost, Fee Structure Overhaul*, PINK SHEET (Sept. 16, 2016), <https://pink.pharmamedtechbi.com/PS119151/Biosimilar-User-Fee-Agreement-Offers-FDA-Funding-Boost-Fee-Structure-Overhaul> [https://perma.cc/MD3W-MSZR]. Not everyone agrees. *E.g.*, Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 61 (2012) ("[C]ompanies are more likely to focus on the development of so-called biodifferents and biobetters (new drugs designed to mimic an existing biological drug), completely forgoing the opportunity to develop biosimilars.").

nism for incentivizing innovative behavior—data exclusivity—is more clearly realized as having a purpose and function different from that of patents. Data exclusivity refers to the period of time before abbreviated applications may be submitted or approved; in the biologic framework, it serves as an incentive for developing new products—that is, for undertaking the safety and effectiveness research necessary for approval of full marketing applications. While novelty informs data exclusivity for drugs, for biologics the inquiry into novelty has been subordinated and mostly relegated to the patent sphere. The task of incentivizing post-approval innovation in biologics has been shifted to the patent system. Patents, in turn, have been lifted out of the regulatory framework; that is, they lack the regulatory significance in the biologic framework that they have in the drug framework.

These differences from the familiar drug paradigm are profound, and their potential significance for innovation and competition should not be under-estimated.

To support these claims, this Article proceeds as follows. Part I describes the shared design and goals of the generic drug and biosimilar biologic statutes. It also explains the scientific considerations relevant to biological medicines and the historical context for enactment of the biosimilar statute, which account for some of its defining characteristics. Part II describes the variability and dynamism of the biologic framework. Section II.A argues that the path to market for biosimilar biologics resembles an innovator's path to market much more than a generic drug applicant's path to market, but notes that the path will vary even now and could become more like the generic path over time. Section II.B argues that the marketplace after biosimilar launch may be utterly unlike the generic marketplace, with different decision-makers driving market penetration and a fair amount of uncertainty today about the factors that will be dispositive. The marketplace combines an apparent need for branding and promotion with the reality of products that may not differ meaningfully in features or labeling. Part III argues that the biologic scheme effects more conceptual and functional separation—than the drug scheme—between patents, on the one hand, and data exclusivity and the regulatory paradigm, on the other hand. Part IV turns briefly to why all of this matters: the possibility that these differences could have a profound effect on the nature and pace of innovation, on the pace of biosimilar development and launch, and on the ways in which firms compete (or fail to compete) in the marketplace. The conclusion is speculative; the actual implications of this sea change in the law of biological medicines remain to be seen and evaluated in the years ahead. The aim of this Article is to serve as a useful framing device for that work.

## II. CONTEXTUALIZING THE BIOSIMILAR STATUTE

For more than a hundred years, the United States has separated its regulation of medicines into parallel but separate tracks. FDA approves non-biological drugs under the Federal Food, Drug, and Cosmetic Act (FDCA) and licenses most biologics under the Public Health Service Act (PHSA).<sup>8</sup>

At a high level, the two statutes take similar approaches to the approval of medicine and aim to further the same basic goals. An innovator will develop a new medicine, establishing its safety and effectiveness for specified medical uses (known as its “indications”) and under specified conditions, through a multi-year process of analytical, preclinical, and clinical testing.<sup>9</sup> FDA will approve the resulting new drug application (NDA) or biologics license application (BLA) when it finds the proposed product safe and effective, applying roughly the same standard to each.<sup>10</sup> The approved product may be associated with a period of data exclusivity. During this time, “abbreviated” applications—for a proposed duplicate or variation of the innovator’s product, known as its “reference” product—may not be submitted to, or approved by, FDA, depending on the provision at issue.<sup>11</sup>

An abbreviated application does not contain data demonstrating the safety and effectiveness of the follow-on product in question; instead it makes a comparative showing sufficient to establish a bridge to the research submitted by the innovator.<sup>12</sup> FDA, when it considers the abbreviated application, relies on the comparative showing, the fact that it approved the reference product, and (indirectly) the research performed by the innovator.<sup>13</sup> The agency approves the follow-on product for some or all of the indications (medical uses), routes of administration (e.g., oral or injectable), dosage forms (e.g., capsule or

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8. FDA approves non-biological drugs under section 505 of the FDCA. 21 U.S.C. § 355 (2012). It licenses biological products under section 351 of the PHSA. 42 U.S.C. § 262 (2012). A handful of proteins currently approved under the FDCA satisfy the definition of “biological product.” Their approved drug applications under the FDCA will be converted to approved biologic applications under the PHSA in 2020. Patient Protection and Affordable Care Act, Pub. L. No. 111-148 § 7002(e)(2), 124 Stat. 119, 817.

9. See generally Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 96-101 (2016) (discussing research and development process).

10. The drug statute requires that a new drug be shown safe and effective, and it requires “substantial evidence” of effectiveness. 21 U.S.C. § 355(d) (2012). The biologic statute requires that a biological product be shown safe, pure, and potent. 42 U.S.C. § 262(a)(2)(C) (2012). FDA interprets the biologic provision as requiring substantial evidence of effectiveness, but it interprets “substantial evidence” more flexibly for biologics than for drugs. 37 Fed. Reg. 16679 (Aug. 18, 1972).

11. FDCA §§ 505(c)(3)(E)(ii)-(iv), (j)(5)(F)(ii)-(iv) (2012); 42 U.S.C. § 262(k)(7) (2012); see Lietzan, *supra* note 9, at 134-61 (describing exclusivity).

12. See Lietzan, *supra* note 9, at 110-21.

13. *Id.* at 104-05.

tablet), and strengths (e.g., 20 mg or 40 mg) of the reference product.<sup>14</sup> In the case of a drug, FDA can also approve variations or changes proposed by the applicant.<sup>15</sup>

The drug statute and biologic statute, and related provisions of the Patent Act, also make it possible for the innovator and follow-on applicant to at least start, if not fully resolve, questions of patent infringement before approval, or perhaps market launch, of the follow-on product.<sup>16</sup>

For a variety of reasons—including the cost-savings achieved through preparation of an abbreviated application—follow-on products may be less expensive for payers, and perhaps also patients, than their reference products. This allows the overall framework to achieve a key goal: cost-savings for the healthcare finance system, once the innovator has had an opportunity to recoup its investment in research and development of the product in the first instance (as well as, perhaps, failed compounds) and to earn a profit sufficient to motivate continued research. These cost-savings can be achieved through direct replacement of higher-priced innovator products with lower-priced duplicates at the point of sale. They can also be achieved through competition for consumers in the marketplace.

Despite their common design and goals, the generic drug framework and biosimilar biologic framework are in fact fundamentally different. There are undoubtedly many explanations for the differences discussed in Part II of this Article. But two threshold observations seem particularly salient.

*First*, as a scientific matter, medicines placed in the “biological product” category differ from medicines regulated as non-biological “drugs.” For FDA regulatory purposes, a “biological product” is a virus, therapeutic serum, antitoxin, vaccine, protein, or analogous product applicable to prevention, treatment, or cure of a disease or condition in humans.<sup>17</sup> The category includes Epogen® (epoetin alfa) (approved for treatment of anemia due to chronic kidney disease or chemotherapy) and Avastin® (bevacizumab) (approved for treatment of various cancers). Both are complex proteins manufactured using biotechnology. The first is a man-made version of a hormone that is ordinarily secreted by the kidneys and that stimulates red cell production. The second is a monoclonal antibody, a type of protein that has no equivalent in the human body and that binds to a specific

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14. 21 U.S.C. § 355(j)(2) (2012); 42 U.S.C. § 262(k)(2) (2012).

15. 21 U.S.C. § 355(b)(2).

16. *Id.* §§ 355(b)(2)-(3), (c)(3), (j)(2)(A)(vii), (j)(2)(B), (j)(5)(B); 42 U.S.C. § 262(l) (2012); 35 U.S.C. § 271(e)(2) (2012).

17. 42 U.S.C. § 262(i) (2012).



substance in the body, usually a protein on the surface of cells. The term “biological product” also includes vaccines, such as Gardasil® (human papilloma virus quadrivalent) (approved for prevention of various cancers), as well as blood products, gene therapy products, and various cell and tissue based products. Medicines that are not placed in the biological product category would include Prozac® (fluoxetine) (approved for treatment of major depressive disorder) and Lipitor® (atorvastatin) (approved to reduce the risk of myocardial infarction and stroke in patients with various risk factors). These are conventional chemically synthesized small molecules. They satisfy the more basic definition of “drug” in the FDCA: any article intended for diagnosis, cure, mitigation, treatment, or prevention of disease.<sup>18</sup> Biological medicines also satisfy that basic definition, but they are first and foremost biologics.<sup>19</sup>

In colloquial terms, the common and distinguishing feature of biologics is that they are often manufactured in, composed of, or derived from, living systems. Biological drugs are usually much larger at the molecular level than non-biological drugs.<sup>20</sup> They are also structurally more complex and sometimes not fully characterized in the laboratory.<sup>21</sup> In some cases, the relationship between a biological product’s

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18. 21 U.S.C. § 321(g) (2012).

19. A biological medicine is subject to the “biological product” provisions of the PHSa (which mainly relate to premarket licensure) and all of the “drug” provisions of the FDCA (unless an exemption, such as the exemption from the NDA requirement, applies). In some cases, depending on what it is and how it works, a biological product could be a device instead of a drug. *See id.* § 321(h) (definition of device).

20. Proteins can be 100 to 1,000 times larger than chemically synthesized molecules. H. Schellekens & James Bausch, *Biopharmaceutical Molecules Are Not Created Equally*, 268 PHARM. J. 300 (2002). Acetaminophen, for example, has a molecular weight of 151 Daltons, while erythropoietin alpha has a molecular weight of 30,400 Daltons. Simon D. Roger, *Biosimilars: How Similar or Dissimilar Are They?*, 11 NEPHROLOGY 341, 342 (2006).

21. Janet Woodcock et al., *The FDA’s Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NATURE REVS. DRUG DISCOVERY 437, 438 (June 2007) (“[P]rotein products are typically much larger, more complex molecules than non-protein, small molecule-drugs and generally cannot be fully characterized using available analytical techniques.”). Dr. Woodcock was the director of FDA’s Center for Drug Evaluation and Research when she authored this piece. Full description of a complex protein typically requires knowledge of its primary structure (linear amino acid sequence linked by peptide bonds), secondary structure (local folding of the amino acid chain into  $\alpha$ -helices,  $\beta$ -pleated sheets, and random coil areas, maintained by hydrogen bonds), tertiary structure (folding of secondary structure into three-dimensional structure, including the formation of disulfide and hydrogen bonds between amino acids), and (when present) quaternary structure (association of multiple subunits of a protein or aggregation of individual proteins). *See generally* FDA, GUIDANCE FOR INDUSTRY, QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY OF A THERAPEUTIC PROTEIN PRODUCT TO A REFERENCE PRODUCT (Apr. 2015) [hereinafter FDA QUALITY CONSIDERATIONS GUIDANCE]; *see also* S.C. Reingold et al., *The Challenge of Follow-On Biologics for Treatment of Multiple Sclerosis*, 73 NEUROLOGY 552 (Aug. 2009); Daan J.A. Crommelin et al., *Shifting Paradigms: Biopharmaceuticals Versus Low Molecular Weight Drugs*, 266 INT’L J. PHARMACEUTICS 3 (2003).

structural attributes and its clinical performance may not be fully understood.<sup>22</sup> In some cases, its mechanisms of action may not be fully understood.<sup>23</sup> As a result of these differences between biologics and other drugs, although the approval standards and data requirements for innovative medicines are generally harmonized as a formal matter, the scientific considerations can differ considerably.<sup>24</sup>

One of the most significant attributes of biological products is their ability to stimulate an immune response in the body. Although some non-biological drugs can be immunogenic, and although some biological medicines (such as vaccines) are purposefully immunogenic, immunogenicity in a therapeutic protein product is usually unintentional and can be concerning. Immune responses can affect both product effectiveness and patient safety.<sup>25</sup> For example, the formation of anti-drug antibodies can neutralize (inactivate) a therapeutic protein, leading to loss of effectiveness. Even when the antibodies are not neutralizing, they can alter the pharmacokinetic profile of the product<sup>26</sup>—for instance, by speeding clearance (which reduces half-life and therefore affects the efficacy profile) in some cases, slowing clearance (and prolonging half-life) in other cases, mistargeting the protein product (reducing efficacy), or promoting other antibody responses.<sup>27</sup> According to FDA, the safety consequences of immunogenicity “may vary wildly and are often unpredictable.”<sup>28</sup> Serious possibilities include anaphylaxis, infusion reactions, and cross-reaction with endogenous counterparts of the therapeutic product.<sup>29</sup>

Product-specific factors—including product origin, product aggregates, impurities with adjuvant activity, formulation, container clo-

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22. FDA, GUIDANCE FOR INDUSTRY, SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT (Apr. 2015) [hereinafter FDA SCIENTIFIC CONSIDERATIONS GUIDANCE].

23. *Id.* at 10.

24. Richard Kingham et al., *Key Regulatory Guidelines for the Development of Biologics in the United States and Europe*, in BIOLOGICAL DRUG PRODUCTS: DEVELOPMENT AND STRATEGIES (Wei Wang & Manmohan Singh eds., 2014).

25. See generally FDA, GUIDANCE FOR INDUSTRY, IMMUNOGENICITY ASSESSMENT FOR THERAPEUTIC PROTEIN PRODUCTS (Aug. 2014), [hereinafter FDA IMMUNOGENICITY GUIDANCE] <https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf> [<https://perma.cc/8KUP-B89Z>].

26. Pharmacokinetics, broadly speaking, is the study of the effect of the body on the drug; pharmacokinetic studies generally measure absorption, distribution, metabolism, and/or excretion of the drug. Jennifer Le, *Overview of Pharmacokinetics*, MERCK MANUAL (last updated Apr. 2016); Gerlie Gieser, *Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development* (PowerPoint), at slide 4.

27. FDA IMMUNOGENICITY GUIDANCE, *supra* note 25, at 3.

28. *Id.*

29. *Id.* (listing less acute possibilities which include: fever, rash, myalgia, hematuria, proteinuria, central nervous system complications, and hemolytic anemia).

sure, and product custody—can increase or decrease the risk of immunogenicity.<sup>30</sup> Put another way, not only does immunogenicity vary by product type (erythropoietin versus tumor necrosis factor inhibitor, for instance), but it can also vary by manufacturer and with manufacturing changes. Johnson & Johnson's experience in the European Union with Eprex® (recombinant human erythropoietin) is instructive.<sup>31</sup> Some patients taking Eprex in the early 2000s in the subcutaneous dosage form to treat anemia associated with chronic renal failure developed neutralizing antibodies to all erythropoietin, including endogenous erythropoietin, which led to a very serious condition, pure red cell aplasia (PRCA). In this condition, the bone marrow stops producing red blood cells. In the late 1990s, the company had substituted polysorbate 80 for human serum albumin, which had previously been used as a stabilizer in its prefilled syringes. The company's investigations showed that uncoated rubber stoppers, when exposed to polysorbate 80, released organic compounds (leachates) into the formulation. Non-clinical testing subsequently indicated that these leachates had weak adjuvant properties, which led the company to identify them as the probable product-specific cause for the increase in erythropoietin antibody-mediated PRCA. Because product-specific factors can increase or decrease the risk, rate, and type of immunogenicity, FDA expects every biologic application—including every biosimilar application—to include an assessment of the product's immunogenicity.<sup>32</sup>

*Second*, not only is the science of biological medicines different, but the context for enactment of the biosimilar statute was different. When Congress enacted the Hatch-Waxman Amendments in 1984, it dropped the legislation into a functional, if weak, generic drug marketplace. Companies had been marketing generic drugs since the

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30. *Id.* at 12-21.

31. See generally Katia Boven et al., *Epoetin-Associated Pure Red Cell Aplasia in Patients with Chronic Kidney Disease: Solving the Mystery*, 20 (Supp. 3) NEPHROLOGY DIALYSIS TRANSPLANTATION iii33, iii34 (2005); see also Johnson & Johnson, Comment Letter on the Passage of the Biologics Price Competition and Innovation Act of 2009 at 2, 3 (Dec. 23, 2010).

32. See generally FDA IMMUNOGENICITY GUIDANCE, *supra* note 25; FDA SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 22, at 16-18; Susan Kirshner, *FDA Immunogenicity Updates*, (PowerPoint), at slide 17 (Feb. 2016), <http://www.e-i-p.eu/wp-content/uploads/2016/03/Susan-Kirschner.pdf> [<https://perma.cc/NR4U-BZ84>] (stating that a biosimilar applicant should assess “the nature of the immune response (e.g., anaphylaxis, neutralizing antibody), the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects), the incidence of immune responses, [and] the population being studied”); see also Leah A. Christl, Janet Woodcock, & Steven Kozlowski, *Biosimilars: The US Regulatory Framework*, 68 ANN. REV. MED. 234, 250 (2016) (“[I]mmunogenicity cannot currently be predicted for complex protein products solely using analytical methods. As a scientific matter, a study assessing immunogenicity is generally expected.”).

1938 enactment of the FDCA. In the early years, these were known as “me too” drugs, and they were brought to market without new drug applications, on the strength of someone else’s research.<sup>33</sup> Although this pathway to market was no longer available by the 1970s, FDA introduced the abbreviated new drug application (ANDA) in the late 1970s, for generic companies seeking to introduce copies of innovative drugs with older NDAs (those reaching the market before 1962). The agency developed therapeutic equivalence ratings at the same time, in response to states that had requested guidance as they implemented laws to encourage generic substitution in order to contain drug costs.<sup>34</sup> The Hatch-Waxman Amendments were enormously important, creating a statutory pathway for copies of newer innovative drugs and creating a scheme for premarket resolution of patent disputes. But the scientific standards and regulatory concepts had already been ironed out in informal rulemaking, and the skeleton for the post-1984 drug marketplace had been in place for years. The agency and industry were ready to launch instantly.

When Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010, by way of contrast, it legislated on a mostly blank slate.<sup>35</sup> The biotechnology industry was only a few decades old, and the first significant recombinant protein products were only beginning to approach patent expiry. The Europeans had authorized only a few comparatively simple biosimilars, and they did so pursuant to legislative authority that essentially allowed the European Medicines Agency (EMA) to fill in the details as it went along. Guidelines issued by the EMA for a few product classes provided U.S. policymakers with templates for consideration, but there was no meaningful experience at FDA for the legislature to draw on. Further, there was no functional U.S. biosimilar industry to engage in the legislative deliberations or to provide real-world experience that could inform the drafting.<sup>36</sup> State pharmacy laws did not address substitution of biological products, nor was there any reason for them to do so. The physician and payer communities had barely begun to think about the prospect of non-innovative biologics. In short, the Congress of the early 1980s took action after FDA had fully devel-

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33. See generally Lietzan, *supra* note 9, at 100-02.

34. See Henry G. Grabowski & John M. Vernon, *Substitution Laws and Innovation in the Pharmaceutical Industry*, 43 LAW & CONTEMP. PROBS. 43 (1979).

35. See generally Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010) (discussing the history of the enacted legislation from 2002 through enactment).

36. Generic drug companies and the generic industry trade association participated in the legislative process on behalf of the nascent biosimilar industry. See generally *id.*

oped the concept of generic drug applications, with a generic industry ready to develop copies of newer products, and with states poised to mandate automatic substitution. The Congress that produced the BPCIA effectively enacted “if we build it they will come” legislation.

### III. COMPETITION: VARIABILITY AND DYNAMISM IN THE BIOLOGIC PATHWAY AND MARKETPLACE

These scientific and historical considerations provide important context for the narrative offered below. As Section III.A explains, largely for scientific reasons, the pathway to market for biosimilar biologics today has more in common with the pathway for innovative biologics than it does with the pathway for generic drugs. The statute’s history means that the basic requirements for market entry are developing while FDA approves the first products, and the scientific context and history together make it likely those requirements will evolve. As Section III.B explains, the resulting marketplace for biosimilars paradoxically combines promotion by sponsors with an apparent lack of product differentiation, and current government reimbursement policies perpetuate this “neither fish nor fowl” aspect of biosimilars. Many factors could affect market penetration, but over time financial considerations—pricing as well as coverage and reimbursement rules—could become paramount. The statute allows FDA to approve a third class of biologics, interchangeable biologics, but there are important unanswered questions about the cost and market impact of interchangeability ratings and, therefore, their appeal to applicants.

#### A. *The Variable and Complex Pathway to Market*

In large part because of the scientific differences between biologics and chemically synthesized drugs, abbreviated applications for biosimilars are more extensive, expensive, and risky than abbreviated applications for generics. Moreover, the pathway will vary from product to product and perhaps from applicant to applicant. In these respects, it is more like the pathway that innovators take.

To begin with, the process is time-consuming, expensive, and risky. An abbreviated application for a biosimilar must show that the proposed biosimilar is highly similar to its reference product and that there are no clinically meaningful differences between the two.<sup>37</sup> The statute calls for analytical studies (showing the two are highly similar notwithstanding minor differences in clinically inactive components), animal studies (including the assessment of toxicity), and at

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37. 42 U.S.C. §§ 262(k)(3), 262(i) (2012).

least one clinical study (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) sufficient to demonstrate safety, purity, and potency in one reference product indication for which licensure is sought.<sup>38</sup> The first biosimilar application approved by FDA included structural and functional characterization, data from five animal studies, and data from eight clinical trials, including two comparative pivotal studies in patients and four pharmacokinetic-pharmacodynamic studies in healthy volunteers.<sup>39</sup> FDA approved this application nearly five years after the applicant and agency met to discuss the applicant's planned clinical program, which followed several years of analytical and pre-clinical work.<sup>40</sup> Hospira's still pending application for biosimilar epoetin alfa reportedly runs "hundreds of thousands of pages."<sup>41</sup>

By way of contrast, a generic drug applicant must prove that the proposed generic is the "same as" and "bioequivalent" to its reference product.<sup>42</sup> That is, the generic drug must have the same active ingredient as well as the same route of administration, dosage form, and strength.<sup>43</sup> Further, there may not be a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose.<sup>44</sup> A senior agency official explained in 2007 that, in contrast with biological medicines, non-biological drugs can usually

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38. *Id.* § 262(k)(2). Pharmacodynamics, broadly speaking, is the study of the effects of a drug in the body, and pharmacodynamic measures are measurements of biological effects that are thought to predict or relate to clinical outcome. Abimbola Farinde, *Overview of Pharmacodynamics*, MERCK MANUAL, <https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacodynamics/overview-of-pharmacodynamics> [<https://perma.cc/H75W-2L44>] (last updated Oct. 2016). For an explanation of pharmacokinetics, see Gieser, *supra* note 26.

39. See generally Sandoz, Advisory Committee Briefing Materials: Available for Public Release, Zarxio® (filgrastim) (Jan. 7, 2015); FDA, SUMMARY REVIEW: BLA 125553 (Mar. 6, 2014).

40. Sandoz and FDA met to discuss proposed clinical testing in September 2010, Sandoz submitted its application in May 2014, and the agency approved the application in March 2015. See FDA, PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION: BLA 125553 (Jan. 30, 2015).

41. Corrected Brief for Defendant-Appellee at 9, *Amgen, Inc. v. Hospira, Inc.*, Docket No. 16-02179 (Fed. Cir. June 7, 2016) (Oct. 25, 2016), at 9 (asserting that Hospira's application contained "over 747,000 pages of information"). FDA has signaled that sponsors may be conducting more studies than strictly needed for approval, and Amgen has claimed that it could have obtained approval of Amjevita on the basis of one phase 3 study but performed a second "to provide added confidence for physicians and patients." Sue Sutter, *Biosimilar Sponsors May Be Going Overboard on Clinical Data, FDA Says*, PINK SHEET (July 13, 2016), <https://pink.pharmamedtechbi.com/PS118756/Biosimilar-Sponsors-May-Be-Going-Overboard-On-Clinical-Data-FDA-Says> [<https://perma.cc/TL43-ZMSP>].

42. 21 U.S.C. § 355(j)(2) (2012).

43. *Id.* § 355(j)(2)(A)(ii), (iii).

44. 21 C.F.R. § 320.1(e) (2016).

be easily characterized, which means making a copy with the same active ingredient is relatively easy.<sup>45</sup> An ANDA generally comprises chemistry, manufacturing, and controls information, including a comparative analytical showing, and modest bioequivalence testing.<sup>46</sup> FDA may not require pre-clinical or clinical safety and effectiveness data.<sup>47</sup>

The differential in cost for applicants is profound. The Federal Trade Commission (FTC) reported in 2009 that generic drug applications typically take three to five years to assemble, with a corresponding cost of \$1 million to \$5 million.<sup>48</sup> It estimated that biosimilar applications would take eight to ten years to develop, with a corresponding cost of \$100 million to \$200 million.<sup>49</sup> Since enactment, biosimilar applicants have confirmed this range.<sup>50</sup> The high cost of developing a biosimilar stems in part from the extensive premarket research and development requirements, but also from the cost and challenge of designing, building, and qualifying a facility capable of reproducibly manufacturing complex and sensitive protein products in compliance with current good manufacturing practices.<sup>51</sup>

The risk in biosimilar research and development has also been manifest. Of the eight biosimilar applications known to have been submitted in 2014 and 2015, more than half were not approved by the initial target dates assigned by FDA.<sup>52</sup> Celltrion received a com-

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45. See Woodcock et al., *supra* note 21, at 437 (“[T]he molecular structure of such a drug can usually be verified analytically [and consequently] it is fairly easy for a generic-drug manufacturer to produce a duplicate product containing an active ingredient that is the same as the active ingredient in an innovator’s approved drug product.”).

46. 21 C.F.R. § 314.94 (contents of an abbreviated application); *id.* pt. 320 (bioavailability and bioequivalence).

47. 21 U.S.C. § 355(j)(2)(A) (2012) (“The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).”).

48. FTC, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION iii (2009).

49. *Id.* In 2015, the Tufts Center for the Study of Drug Development estimated \$75 to \$250 million for biosimilars. TUFTS CTR., TUFTS CSDD IMPACT REPORT, Vol. 17, No. 2 (Apr. 2015).

50. Hospira, which submitted an application to FDA in 2015 for Retacrit®, a biosimilar epoetin alfa product, projected average costs from \$100 million to \$200 million. *Developing Biosimilars*, HOSPIRA, <http://www.hospira.com> (last visited May 9, 2017). Celltrion stated in March 2014 that it had spent \$112 million developing its biosimilar infliximab product. Complaint for Declaratory Judgment at 8, *Celltrion Healthcare Co. v. Janssen Biotech, Inc.*, No. 14-11613 (D. Mass.) (Mar. 31, 2014).

51. See Henry Grabowski & Erika Lietzan, *FDA Regulation of Biosimilars*, in *FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* (Lynch & Cohen eds., 2015).

52. See *Pending Biosimilars: Biosimilar Applications Submitted to FDA*, PINK SHEET (Sept. 26, 2016) (providing a table with status of all known biosimilar applications). When FDA accepts an application for review, it sets the target date for its decision, also known as the application’s “action date.” As a general rule, the action date is ten months later. The ten-month cycle was negotiated with the biosimilar industry in connection with statutory

plete response letter—meaning that FDA could not approve the application—because deficiencies in the analytical data precluded a finding that its biosimilar infliximab product was highly similar to Remicade.<sup>53</sup> The company provided data to address the deficiencies, leading to approval in a second review cycle.<sup>54</sup> Hospira similarly received a complete response letter regarding its biosimilar epoetin alfa application.<sup>55</sup>

Unlike the contents of generic drug applications, the contents of biosimilar applications—and therefore the time investment, cost, and, perhaps, risk involved—may also vary for the foreseeable future. There are two reasons for this.

*First*, the data and information needed to support approval as a biosimilar may differ from product type to product type, in part because the characteristics that distinguish biologics from chemically synthesized drugs may also distinguish one biologic from the next. Thus, when describing the obligations of biosimilar applicants, FDA has noted that different protein products may be more or less well characterized structurally or functionally.<sup>56</sup> There may be varying degrees of understanding of the relationship between their structural attributes and their clinical performance. Their mechanisms of action may or may not be well understood, and some may have more than one. The pathologies of the diseases they treat may be more or less well understood. There may be considerable or only modest clinical experience with the product class. There may or may not be relevant pharmacodynamic measures. There may or may not be a meaningful correlation between pharmacodynamic and pharmacokinetic results, on the one hand, and clinical effectiveness, on the other hand. Features relevant to clinical trial design, like half-life and immunogenicity, may vary. All of these considerations influence how one would show that two such products are similar. Consequently, the data and information needed for biosimilar approval will vary.<sup>57</sup>

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authorization to assess user fees. FDA, BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017; FDA MANUAL OF POLICIES AND PROCEDURES, MAPP 6020.8, REV. 1 (June 13, 2016).

53. See FDA, MEDICAL OFFICER REVIEW: BLA 125544, at 2 (Apr. 5, 2016) [hereinafter FDA, MEDICAL OFFICER REVIEW]; see also 21 C.F.R. § 601.3 (2016) (describing complete response letters).

54. See FDA, MEDICAL OFFICER REVIEW, *supra* note 53, at 2.

55. Sue Sutter, *Biosimilar Denied: Hospira's Retacrit Could Head Back to FDA in First Half 2016*, PINK SHEET DAILY (Oct. 27, 2015), <https://pink.pharmamedtechbi.com/PS077926/Biosimilar-Denied-Hospiras-Retacrit-Could-Head-Back-To-FDA-In-First-Half-2016> [<https://perma.cc/ZW93-M88S>].

56. See generally FDA, SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 22.

57. The EMA has issued detailed guidelines specific to biosimilar products containing recombinant follicle-stimulating hormone, interferon beta, monoclonal antibodies, recom-



*Second*, the data and information necessary for approval as a biosimilar may also vary from applicant to applicant within a product class. This is because FDA has embraced a “stepwise approach” to demonstrating biosimilarity.<sup>58</sup> The essence of this approach is moving systematically from comparison of structure and function, to comparison of animal toxicity, to comparative human pharmacokinetic and pharmacodynamics studies, to comparative clinical immunogenicity studies, and then ultimately (and only if necessary) to comparative clinical safety and effectiveness trials.<sup>59</sup> After each step, FDA has explained, the applicant should “evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty.”<sup>60</sup> At various milestones in the stepwise process, the agency provides advice to the applicant after reviewing the data and information collected to date.<sup>61</sup> Thus, application requirements are tailored not only to the product type, but also to the applicant’s findings and the agency’s input at each step. FDA has launched a “biosimilar development program,” supported by user fees, to facilitate this collaborative process.<sup>62</sup> While modifying an overall product development program as one proceeds and depending on one’s results is standard fare for innovators, it may add to the variability in application contents, cost, and timing for biosimilar applicants and has no meaningful counterpart in the generic drug paradigm.<sup>63</sup>

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binant erythropoietin, low molecular weight heparin, interferon alpha, recombinant granulocyte-colony stimulating factor, somatropin, and recombinant human insulin and insulin analogues. These guidelines describe the preclinical and clinical studies necessary and provide specific information about study design, such as route of administration, subject selection, dosing regimen, duration of trial, primary and secondary endpoints, and data analysis. The designs vary considerably. *Compare* GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS (REVISION), EMEA/CHMP/BMWP/301636/2008 (Mar. 18, 2010), with GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING INTERFERON BETA, EMA/CHMP/BMWP/652000/2010 (Feb. 21, 2013).

58. See FDA SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 22, at 2, 7-8.

59. *Id.* at 9-22.

60. *Id.* at 7.

61. *Id.* at 8.

62. See generally FDA, GUIDANCE FOR INDUSTRY: FORMAL MEETINGS BETWEEN THE FDA AND BIOSIMILAR BIOLOGICAL PRODUCT SPONSORS OR APPLICANTS (Nov. 2015); see also 21 U.S.C. § 379j-52(a)(1) (2012).

63. Bioequivalence testing requirements vary but stay within certain basic parameters. For instance, the agency might permit *in vitro* dissolution testing rather than requiring *in vivo* pharmacokinetic measurements, it might require both fasting and fed conditions for an oral product, or it might develop a special approach for an inhaled or topical product. *Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient*, FDA <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm> [https://perma.cc/N4Y6-YBBR] (last updated Nov. 15, 2017).

Like innovators, some biosimilar applicants may be able to minimize their overall premarket burden by submitting the same clinical trials to different regulators. This is because regulators in the developed world—not only the EMA, Health Canada, and FDA, but also Japan’s Ministry of Health, Labor, and Welfare (MHLW), and the Australian Therapeutic Goods Administration (TGA), among others—are taking similar approaches to biosimilar approval, much as they do with innovative drug and biologic approval, and much as they did with generic drug pathways in the 1980s.<sup>64</sup> Like FDA, these regulators generally require a high degree of analytical similarity, some premarket clinical immunogenicity data, comparative pharmacokinetic and pharmacodynamic data, and at least one comparative clinical trial using an endpoint that reflects a reference product indication.<sup>65</sup> Because regulators are generally aligning in approach, biosimilar applicants have sought to persuade regulators to accept at least some of the same data.<sup>66</sup> Because biosimilar applications are compar-

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64. See Barbara Mounho et al., *Global Regulatory Standards for the Approval of Biosimilars*, 65 FOOD & DRUG L.J. 819 (2010); Peter Bogaert, Erika Lietzan & Laura Sim, *Biosimilar Regulation: Important Considerations and Global Developments*, PLC LIFE SCI. HANDBOOK (2011), <https://www.cov.com/~media/files/corporate/publications/2011/01/biosimilar-regulation---important-considerations-and-global-developments---2011.pdf> [https://perma.cc/DK5M-3BQ3].

65. Mounho et al., *supra* note 64. As a group of biostatisticians from FDA recently explained, this does not mean that the trials must use the same endpoints as an innovator would use. The primary goal of the comparative clinical study is to support a finding that there are no clinically meaningful differences between the products. In a non-inferiority trial to support a pioneer product, by way of contrast, the endpoint must also establish treatment effect. This means an interim or surrogate endpoint might be acceptable in a clinical study for biosimilar approval, where a clinical endpoint would be necessary for approval of an innovative produce. See Kun He et al., *Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study*, 22 CLINICAL CANCER RES. 5167 (2016).

66. See, e.g., GPHA, Comment Letter on Implementation of New Abbreviated Biogeneric Pathway Created in the Biologics Price Competition and Innovation Act of 2009, (Dec. 30, 2010) (“Clearly, one of the most immediate ways for FDA to be proactive is to support biogeneric applicants using data previously generated outside the U.S. in other highly regulated markets, and encourage them to appropriately build on these studies and provide justification or add additional data that appropriately connects the EU efforts to the chosen US 351(a) reference product. The entirety of this data set then forms the US biogeneric application.”); Novartis, Comment Letter on Implementation of New Abbreviated Biosimilar Pathway Created in the Biologics Price Competition and Innovation Act of 2009 (Dec. 30, 2010) at 20 (“Therefore, to the extent that any biosimilar has been developed and used in another market in which comparable regulatory standards and procedures apply, the data on its development and prior use can be of great value to the FDA in evaluating the same candidate product for use in the U.S.”); Derrick Gingery, *Biosimilar Market Formation Isn’t Going According to Plan*, PINK SHEET DAILY (Dec. 18, 2015), <https://pink.pharmamedtechbi.com/PS078099/Biosimilar-Market-Formation-Isnt-Going-According-To-Plan> [https://perma.cc/C6HM-SLE4] (noting that FDA had not expected so many sponsors to seek agency development advice even though they would not submit a U.S. application for years, and adding that “sponsors are conducting global development programs and want to ensure they will be compliant in the U.S., even though they may file for approval somewhere else first”).

ative applications, as a practical matter this means submitting to one regulator data from clinical trials that used—as a comparator—a version of the innovator’s product approved by a different regulator.<sup>67</sup> The EMA and FDA will permit use of non-local comparator products for some studies supporting biosimilar approval, if certain conditions are met, and Health Canada plans the same.<sup>68</sup> Thus, for example, the U.S. application for Inflectra contained only one clinical study with U.S.-approved Remicade: a single-dose pharmacokinetic study in 213 healthy volunteers.<sup>69</sup>

Fully global applications may not be possible, however. Legal considerations might require U.S. applicants to use the U.S. reference product in at least one trial.<sup>70</sup> Also, regulators may have differing views of the scientific issues raised by studies, as diverging reactions to the biosimilar infliximab applications demonstrate.<sup>71</sup> Whether and to what extent biosimilar applicants will be able to minimize their

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67. Use of a foreign-approved comparator product in a trial for domestic approval is different from submitting data from trials conducted in non-U.S. populations in non-U.S. locations. In the first example, a company is using, as the control in its trial, a product that FDA has not approved. This trial could occur anywhere in the world, including in the United States. In the second example, the company is using an FDA-approved product as the control, but the trial *site* is in another country. FDA refers to the latter as a “foreign clinical study.” See 21 C.F.R. § 312.120 (2016) (governing submission of data from foreign clinical studies).

68. FDA, GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (Apr. 2015), at 8 [hereinafter FDA Q&A GUIDANCE]; EMA, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS, CHMP/437/04 REV. 1 (Oct. 23, 2014) § 3.2 [hereinafter EMA OVERARCHING GUIDELINE]; HEALTH CANADA, DRAFT-REVISED GUIDANCE DOCUMENT: INFORMATION AND SUBMISSION REQUIREMENTS FOR BIOSIMILAR BIOLOGIC DRUGS § 2.1.3 (Nov. 14, 2015).

69. See Celltrion, Advisory Committee Briefing Materials: Available for Public Release: CT-P13 (infliximab biosimilar) 71 (Feb. 9, 2016).

70. The PHSA requires comparison with a product licensed by FDA. See 42 U.S.C. § 262(i)(4) (2012).

71. Remicade (infliximab) is approved for eight indications in two categories: rheumatic and related diseases (like rheumatoid arthritis) and inflammatory bowel diseases (like Crohn’s Disease). Celltrion performed a pivotal comparative efficacy and safety study in patients with rheumatoid arthritis, as well as a pivotal comparative pharmacokinetic study in patients with ankylosing spondylitis. Although Celltrion studied only two uses, the European Commission authorized Remsima for all eight, using a process known as “extrapolation.” This allows an applicant to submit a scientific argument that the showings already made (a lack of clinically meaningful differences with respect to one patient population and indication, plus the balance of the data package, including analytical data) justify extrapolating to approval for additional populations and indications. FDA took the same approach. Health Canada, however, approved Remsima for only the four rheumatic indications. It denied the four gastrointestinal indications, identifying differences between the products that “could have an impact on the clinical safety and efficacy of these products in these indications.” HEALTH CANADA, SUMMARY BASIS OF DECISION FOR REMSIMA (Apr. 1, 2014); see also Feagan et al., *The Challenge of Indication Extrapolation for Infliximab Biosimilars*, 42 *BIOLOGICALS* 177, 178 (2014).

premarket burden by harmonizing application packages in differing jurisdictions, as innovators often can, remains to be seen and—as the infliximab experience suggests—may vary from product to product.

Table 1 illustrates the variability of the biologic framework, using publicly available information about the first four approved biosimilar biologics. The variability is manifest; the number of preclinical studies varies; the number of clinical pharmacokinetic studies varies; and the number, size, and length of clinical efficacy studies vary. For instance, the first application (Zarzio) contained a pivotal clinical safety and efficacy study using the U.S.-approved reference product; none of the rest did. The fourth application (Amjevita) contained fewer animal and human pharmacokinetic studies, but the sponsor included two clinical efficacy studies. One biosimilar was studied in 683 subjects, another in over 1000. One pivotal study lasted 77 weeks, and another 26 weeks.

Description	<b>Zarzio</b>	Filgrastim is a hormone-like growth factor required for the growth and development of hematopoietic progenitor cells.
	<b>Inflectra</b>	Infliximab is a monoclonal antibody that targets tumor necrosis factor.
	<b>Erelzi</b>	Etanercept is a fusion protein that targets tumor necrosis factor.
	<b>Amjevita</b>	Adalimumab is a monoclonal antibody that targets tumor necrosis factor.
Preclinical studies	<b>Zarzio</b>	Five animal studies comparing Zarzio with EU Neupogen, assessing toxicity, toxicokinetics, local tolerance, and pharmacodynamics.
	<b>Inflectra</b>	One human tissue and five animal studies (three compliant with good laboratory practices), comparing Inflectra and EU Remicade, assessing pharmacology, pharmacokinetics, toxicology, and toxicokinetics.
	<b>Erelzi</b>	<ul style="list-style-type: none"> <li>• One dose-finding study in mice</li> <li>• Four animal studies comparing Erelzi with EU Enbrel, assessing PD, PK, and toxicity including local tolerance and immunogenicity</li> </ul>

72. The information in this table is taken from the sponsor and agency briefing materials prepared for the advisory committee meetings considering the applications in question, and, where available, on Drugs@FDA, the review documents.

	<b>Amjevita</b>	Two animal studies comparing Amjevita with US Humira, pme assessomg toxicokinetics and the other assessing toxicity and toxicokinetics.
Clinical PK/PD studies	<b>Zarzio</b>	<ul style="list-style-type: none"> <li>• One PK/PD study in healthy volunteers comparing Zarzio with US Neupogen (pivotal study)</li> <li>• Four PK/PD studies in healthy volunteers comparing Zarzio with EU Neupogen</li> </ul>
	<b>Inflectra</b>	<ul style="list-style-type: none"> <li>• One PK/PD study comparing Inflectra, EU Remicade, and US Remicade, in healthy subjects (pivotal study)</li> <li>• One PK study comparing Inflectra and EU Remicade in patients with ankylosing spondylitis (AS) (pivotal study)</li> <li>• An open-label extension of the AS study</li> </ul>
	<b>Erelzi</b>	<ul style="list-style-type: none"> <li>• Three PK studies in healthy subjects; two compared Erelzi with EU Enbrel, and one compared Erelzi with US Enbrel</li> <li>• One cross-study comparison of two studies in the last bullet, to establish a bridge from EU Enbrel to US Enbre.</li> <li>• An open-label cross-over study of Erelzi using two different devices</li> </ul>
	<b>Amjevita</b>	One PK study comparing Amjevita, US Humira, and EU Humira in healthy volunteers.
Clinical safety and efficacy studies	<b>Zarzio</b>	<ul style="list-style-type: none"> <li>• One randomized, double-blind study comparing Zarzio and US Neupogen in patients with breast cancer (pivotal study)</li> <li>• Two open-label, single-arm studies of Zarzio, one in breast cancer patients and one in healthy stem cell donors</li> </ul>
	<b>Inflectra</b>	<ul style="list-style-type: none"> <li>• One randomized, double-blind study comparing Inflectra and EU Remicade in patients with rheumatoid arthritis (RA) (pivotal study)</li> <li>• An open-label extension of the RA study</li> <li>• A pilot study comparing Inflectra and EU Remicade in RA patients in the Philippines, two double blind studies (in Russia and in Japan) comparing Inflectra and EU Remicade in RA patients,</li> </ul>

		and an open label extension of the Japan study
	<b>Erelzi</b>	One randomized, double-blind study comparing Erelzi with EU Enbrel in patients with plaque psoriasis.
	<b>Amjevita</b>	<ul style="list-style-type: none"> <li>• One randomized, double-blind study comparing Amjevita and US Humira in patients with RA</li> <li>• One randomized, double-blind study comparing Amjevita with EU Humira in patients with plaque psoriasis</li> </ul>
Duration of pivotal clinical efficacy and safety study or studies	<b>Zarzio</b>	77 weeks
	<b>Inflectra</b>	54 weeks
	<b>Erelzi</b>	52 weeks
	<b>Amjevita</b>	<ul style="list-style-type: none"> <li>• 26 weeks (RA)</li> <li>• 52 weeks (plaque psoriasis)</li> </ul>
Total number of patients enrolled in submitted trials	<b>Zarzio</b>	<ul style="list-style-type: none"> <li>• 174 healthy volunteers</li> <li>• 388 breast cancer patients receiving myelosuppressive chemotherapy</li> <li>• 121 healthy stem cell volunteers</li> </ul>
	<b>Inflectra</b>	<ul style="list-style-type: none"> <li>• 213 healthy volunteers</li> <li>• 606 patients with rheumatoid arthritis</li> <li>• 250 patients with ankylosing spondylitis</li> </ul>
	<b>Erelzi</b>	<ul style="list-style-type: none"> <li>• 216 healthy volunteers</li> <li>• 531 patients with plaque psoriasis</li> </ul>
	<b>Amjevita</b>	<ul style="list-style-type: none"> <li>• 203 healthy subjects</li> <li>• 467 patients with rheumatoid arthritis</li> <li>• 350 patients with plaque psoriasis</li> </ul>
Studies using the U.S.-licensed reference product	<b>Zarzio</b>	<ul style="list-style-type: none"> <li>• One PK/PK study</li> <li>• One clinical safety and efficacy study</li> </ul>
	<b>Inflectra</b>	One PK/PD study
	<b>Erelzi</b>	One PK study (and the preplanned cross study report)
	<b>Amjevita</b>	<ul style="list-style-type: none"> <li>• One PK study</li> <li>• One clinical safety and efficacy study</li> </ul>
Number of indications (or patient populations studied) & number of indications	<b>Zarzio</b>	<ul style="list-style-type: none"> <li>• One patient population studied</li> <li>• Five indications approved</li> </ul>
	<b>Inflectra</b>	<ul style="list-style-type: none"> <li>• Two patient populations studied</li> <li>• Seven indications approved</li> </ul>
	<b>Erelzi</b>	<ul style="list-style-type: none"> <li>• One patient population studied</li> <li>• Five indications approved</li> </ul>

**Table 1: Comparison of Biosimilar Applications**<sup>72</sup>

approved	<b>Amjevita</b>	<ul style="list-style-type: none"> <li>• Two patient populations studied</li> <li>• Seven indications approved</li> </ul>
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The data and information necessary for licensure as a biosimilar are likely to change over time. The Europeans, who began authorizing biosimilars in 2006, have already reworked several of their basic framework guidelines, including the general guidelines on analytical testing and on non-clinical and clinical testing.<sup>73</sup> They have also reworked—or are in the process of reworking—some of the class-specific guidelines, such as the guidelines for biosimilar erythropoietin and granulocyte-colony stimulating factor.<sup>74</sup> FDA’s expectations will surely evolve over time, as well, and the statute is written to accommodate this evolution.<sup>75</sup> Moreover, the two regulators have established a working group for collaboration on biosimilar issues, with the express goal of avoiding “regulatory divergence” that may delay access to medicines.<sup>76</sup> On the whole, the EMA seems to be taking a less conservative approach than it did in 2006.<sup>77</sup> Collaboration with the EMA could influence FDA to become less conservative, itself, over time.<sup>78</sup> The agency has already signaled intent to minimize the ani-

73. EMA OVERARCHING GUIDELINE, *supra* note 68 (revising earlier version adopted in September 2005); EMA, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES, EMA/CHMP/BWP/247713/2012 REV. 1 (May 22, 2014) (revising earlier version adopted in February 2006); EMA, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES, EMEA/CHMP/BMWP/42832/2005 REV. 1 (Dec. 18, 2014) (revising earlier version adopted in February 2006).

74. *See, e.g.*, EMA, CONCEPT PAPER ON THE REVISION OF THE GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR, EMA/CHMP/BMWP/214262/2015 (July 23, 2015).

75. The statute lays out a default of analytical, animal, and clinical studies, adding that FDA may determine that any of these elements is “unnecessary” in a particular application. 42 U.S.C. § 262(k)(2)(A)(ii) (2012).

76. FDA, *European Commission and EMA Reinforce Collaboration to Advance Medicine Development and Evaluation*, EUR. MEDS. AGENCY (July 14, 2015), [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2015/07/news\\_detail\\_002367.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002367.jsp&mid=WC0b01ac058004d5c1) [https://perma.cc/RMN9-83TB].

77. The class-specific guidance documents have become more detailed and prescriptive, but the overarching guideline now states that, in some situations, pharmacodynamic endpoints may suffice and a clinical efficacy trial may not be needed. EMA OVERARCHING GUIDELINE, *supra* note 68, § 3.3; *see also* Ian Schofield, *Biosimilars in EU Seeing Reduced Clinical Data Requirements*, PINK SHEET (May 13, 2016), <https://pink.pharmamedtechbi.com/PS079399/Biosimilars-In-EU-Seeing-Reduced-Clinical-Data-Requirements> [https://perma.cc/39H4-W4EK].

78. FDA is generally more conservative than its European counterpart, however. *See, e.g.*, W. Kip Viscusi & Richard J. Zeckhauser, *Regulating Ambiguous Risks: The Less Than Rational Regulation of Pharmaceuticals*, 44 J. LEGAL STUD. S387, S389-90 (2015) (noting

mal and clinical studies necessary for licensure.<sup>79</sup> And the stepwise approach described in its guidance is essentially a front-loaded and iterative application process designed to accomplish precisely this result.

How quickly the U.S. requirements change, whether they change across the board or for some product types more quickly than others, and just how much they will change remains to be seen. By way of contrast, though, the basic approach to generic drug approval has not changed meaningfully in thirty years.

### B. *Neither Fish nor Fowl in the Marketplace*

The marketplace of biologics and biosimilars may differ profoundly from the marketplace of innovative drugs and generic drugs. Biosimilars are, to borrow an old English proverb, neither fish nor fowl.<sup>80</sup> They will be presented and treated both like, and unlike, innovative products.

#### 1. *The Inapplicability of the Generic Market Penetration Model*

When FDA approves a generic drug, it issues a “therapeutic equivalence” rating, indicating whether, in its judgment, the generic can be substituted for a prescribed reference product, “with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.”<sup>81</sup> The agency designates a generic drug as therapeutically equivalent to its reference drug—gives it an “A” rating in the *Orange Book*—if the two are “pharmaceutical equivalents” and “can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”<sup>82</sup> In particular, the two must have the same active ingredient, route of administration, dosage form, and strength, and they must be bioequivalent.<sup>83</sup> These are the same as the requirements for generic drug approval in the first instance.<sup>84</sup> Thus, a generic drug is, by definition, therapeutically equiv-

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perceived drug lag between the United States and Europe, ranging in time from a study in 1980 to an example from 2002). Divergence between the two regulators therefore remains possible.

79. See, e.g., FDA SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 22, at 13-14.

80. See MORRIS P. TILLEY, A DICTIONARY OF THE PROVERBS IN ENGLAND IN THE SIXTEENTH AND SEVENTEENTH CENTURIES 218-19 (1950).

81. FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS vii-viii (36th ed. 2016) [hereinafter ORANGE BOOK].

82. *Id.* at vii.

83. *Id.*

84. 21 U.S.C. § 355(j)(2)(A) (2012).



alent to its reference product.<sup>85</sup> No additional showing needs to be made.

By way of contrast, biosimilar biologics are not inherently therapeutically equivalent to their reference products. Congress actually created two new types of biologics in 2010: biosimilar biologics and interchangeable biologics.<sup>86</sup> Interchangeable biologics are subject to a different standard of approval.<sup>87</sup> The sponsor of an interchangeable biologic must show not only that its product is biosimilar, but also that its product can be expected to produce the same clinical result in any given patient and, in the case of a product administered more than once to a patient (true of most therapeutic proteins), that the risk of alternating or switching between the products is no greater than the risk of using the reference product alone.<sup>88</sup> An interchangeable biologic—not a biosimilar biologic—“may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”<sup>89</sup> This makes interchangeability determinations for biologics analogous to therapeutic equivalence ratings for drugs, and interchangeable biologics—not biosimilar biologics—analogueous to generic drugs.

Market penetration by generic drugs is both swift and automatic. When a prescriber specifies a brand product, state pharmacy law generally leads the dispensing pharmacist to substitute an A-rated generic drug.<sup>90</sup> An examination of new molecular entities experiencing initial generic entry in 2011 and 2012 found that the average brand retained only 16% of the market after one year.<sup>91</sup> The same study also found that one-year market erosion had increased dramatically over the preceding decade.<sup>92</sup> Another study found that six drugs

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85. A generic drug approved pursuant to a suitability petition (with a variation in route of administration, dosage form, or strength or in one of two active ingredients) is not therapeutically equivalent. See *infra* note 105.

86. Compare 42 U.S.C. § 262(k) (2012) (“Licensure of biological products as biosimilar or interchangeable.” (emphasis added)), with *id.* § 262(i)(2) (defining biosimilar biologic), with (i)(3) (defining interchangeable biologic).

87. Compare *id.* §§ 262(k)(2) (describing biosimilar application contents), and 262(k)(3) (laying out biosimilar standard of approval), with (k)(4) (interchangeability standard of approval).

88. *Id.* § 262(k)(4).

89. *Id.* § 262(i)(3).

90. State laws vary. Some explicitly cross-reference the *Orange Book*, while others refer to therapeutic equivalents, and others refer to generics. Some states characterize substitution as permissive, and others characterize it as mandatory, albeit subject to override by the treating physician. See *New York v. Actavis*, 787 F.3d 638, 645 (2d Cir. 2015) (describing variation in state substitution laws).

91. Henry Grabowski et al., *Recent Trends in Brand-Name and Generic Drug Competition*, 17 J. MED. ECON. 207, 212 (2014).

92. *Id.*

that lost exclusivity between 2009 and 2013 lost 60% of their market share within (on average) three months of generic entry.<sup>93</sup> Automatic therapeutic equivalence ratings, working in concert with state pharmacy laws, drive this rapid generic market penetration. In contrast, because biosimilar biologics will not be deemed interchangeable by FDA or substitutable under state pharmacy laws, they must achieve market penetration differently.<sup>94</sup> If a biosimilar is to be dispensed to a patient, it must be prescribed—selected by a treating physician for that patient. State law will not make the choice automatically.

## 2. *Decisionmakers Influencing Market Penetration*

The patient's healthcare provider is only one of the parties playing a role in the choice of medicine for any particular patient. Payers will also play a pivotal role, including through the decisions made by their formulary committees. A formulary is a list of medicines for use in prevention, treatment, or cure of diseases and conditions.<sup>95</sup> Many entities involved in healthcare delivery and finance—including hospitals, other inpatient facilities, Medicaid,<sup>96</sup> Medicare,<sup>97</sup> private insurance companies, pharmacy benefit managers, employers, and managed care organizations—use formularies as a way to manage costs while ensuring safe and effective treatment of patients.<sup>98</sup> A formulary committee will make the basic coverage decision about a biosimilar, and it may influence market penetration with the cost-management strategies that it adopts.<sup>99</sup>

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93. Murray L. Aitken et al., *The Regulation of Prescription Drug Competition and Market Responses: Patterns in Prices and Sales Following Loss of Exclusivity* 6-7 (Nat'l Bureau of Econ. Research, Working Paper No. 19487 2013), <http://www.nber.org/papers/w19487.pdf> [<https://perma.cc/KS8G-XFWC>].

94. States are amending their pharmacy laws to address biologic substitution, just as those laws currently authorize drug substitution. *See, e.g.*, DEL. CODE ANN. tit. 24, § 2549A (2016); FLA. STAT. § 465.0252 (2016); IND. CODE § 16-42-25-4 (2016); MASS. GEN. LAWS ch. 112, § 12EE (2016); N.D. CENT. CODE § 19-02.1-14.3 (2016); OR. REV. STAT. § 689.522 (2016); UTAH CODE ANN. § 58-17b-605.5 (2015); VA. CODE ANN. § 54.1-3408.04 (2016). None of the new laws deems *biosimilar* biologics substitutable; instead, they authorize substitution of *interchangeable* biologics.

95. ACAD. OF MANAGED CARE PHARMACY (AMCP), FORMULARY MANAGEMENT (2009), <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9298> [<https://perma.cc/HXX3-7TUR>].

96. Medicaid, which funds health care for persons of limited means, is administered by the states and funded by the state and federal governments together. *See generally* 42 U.S.C. § 1396 (2012). Each state prepares its own plan, which must comply with federal law and regulations.

97. Medicare is the federally funded health insurance program for persons over 65 years of age (and certain younger persons with disabilities). *See generally id.* § 1395.

98. AMCP, *supra* note 95.

99. *See generally* JACK HOADLEY, KAISER FAMILY FOUND., THE EFFECT OF FORMULARIES AND OTHER COST MANAGEMENT TOOLS ON ACCESS TO MEDICATIONS: AN ANALYSIS OF THE MMA AND PROPOSED REGULATIONS (2004), <https://kaiserfamilyfoundation.files.wordpress.com/>

To begin with, a formulary committee might simply decline to cover the reference product, excluding the product from coverage and listing only the biosimilar.<sup>100</sup> Or a formulary committee might adopt a tiered formulary to drive patients to the biosimilar. In this layered approach to cost-sharing, a preferred medication (the biosimilar) is placed in a tier that involves lower costs for the patient, while a non-preferred medication (the reference product) is placed in a higher-cost tier.<sup>101</sup> Or the committee might impose a “prior authorization” requirement, so that the patient must obtain permission before a particular medication (the reference product) will be covered.<sup>102</sup> Further, it could impose therapeutic interchange, sometimes called non-medical switching or therapeutic substitution. This entails switching a patient between unrelated products in the same therapeutic class—i.e., authorizing the pharmacist to dispense a formulary-listed therapeutic alternative (the biosimilar) in place of a non-formulary medication or a non-preferred formulary medication (the reference product) without contacting the prescriber.<sup>103</sup> Therapeutic interchange in the biologic context could mean dispensing a biosimilar in lieu of the reference product or instead of another product in the same class—dispensing Zarxio (filgrastim-sndz) instead of Neupogen (filgrastim), its reference product, or instead of Granix® (tbo-filgrastim), another innovative filgrastim product, or indeed instead of Neulasta (pegfilgrastim), a newer innovative product in the same class.

In short, although the physician plays the primary formal role in selection of a patient’s treatment in the biologic framework, another entity involved in healthcare delivery and finance may force or at least profoundly influence the choice. Formulary committees could, in

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2013/01/the-effect-of-formularies-and-other-cost-management-tools-on-access-to-medications-an-analysis-of-the-mma-and-proposed-regulations.pdf [https://perma.cc/65ZC-LA3G]. Formulary committees are also known as “pharmacy and therapeutics committees” or “P&T committees.”

100. CVS/Caremark, which covers 75 million Americans, took precisely this approach in its 2017 formulary, dropping Neupogen in favor of its biosimilar Zarxio. *2017 Formulary Strategy*, CVS HEALTH (Aug. 5, 2016), <http://insights.cvshealth.com/sites/default/files/cvs-health-insights-2017-formulary-strategy-overview-august-2016.pdf>; Alison Kodjak, *Will Your Prescription Meds Be Covered Next Year? Better Check!*, NPR HEALTH SHOTS (Aug. 15, 2016, 4:32 AM), <http://www.npr.org/sections/health-shots/2016/08/15/489790412/will-your-prescription-meds-be-covered-next-year-better-check>.

101. *See, e.g.*, AMGEN, 2016 TRENDS IN BIOSIMILARS REPORT 25-26 (2016) (discussing possibility of tiering).

102. AMCP, PRIOR AUTHORIZATION (2012), [http://www.amcp.org/prior\\_authorization/](http://www.amcp.org/prior_authorization/) [https://perma.cc/P232-RM5G].

103. *See* AM. SOC’Y OF HEALTH-SYS. PHARMACISTS, ASHP GUIDELINES ON THE PHARMACY AND THERAPEUTICS COMMITTEE AND THE FORMULARY SYSTEM 212 (2008), <https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/gdl-pharmacy-therapeutics-committee-formulary-system.ashx?la=en&hash=EF1E4214CC91C65097AEECE91BF6EC985AE3E56> [https://perma.cc/TFY8-5THZ].

a sense, play the role for biosimilars that state substitution laws play for generic drugs.

### 3. *Factors Affecting Market Penetration*

When considering their choices, physicians and payers will be choosing among products that, by law, are not meaningfully different. Financial considerations are thus likely to be paramount.

#### (a) *Lack of Meaningful Differences*

The primary features of a biosimilar must be the same as those of the reference product; the statute requires that it have the same route of administration, dosage form, and strength.<sup>104</sup> The biologic statute is less flexible in this regard than the drug statute. Although a generic drug must ordinarily have the same route of administration, dosage form, and strength as its reference product, the applicant may vary any of these features and still file an ANDA if FDA has approved a “suitability” petition.<sup>105</sup> The agency must in turn approve this petition unless it concludes that new safety or effectiveness studies would be needed.<sup>106</sup> There is no comparable option in the biologic statute, which means that if these features are changed, a biosimilar application is not permitted.

In addition, a generic drug applicant may vary *any* aspect of the innovative product and still file an abbreviated application, under a *different* provision of the Hatch-Waxman Amendments. The resulting application, known as a “505(b)(2) application” rather than an ANDA, is a hybrid application. It is partially generic (relying on an earlier innovator’s research) and partially innovative (supporting new features with original research).<sup>107</sup> The ANDA is less expensive and generally leads to an automatically substitutable product, but the 505(b)(2) pathway is *always* available to a generic applicant.<sup>108</sup> A ge-

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104. 42 U.S.C. § 262(k)(2)(A)(i)(IV) (2012).

105. 21 U.S.C. §§ 355(j)(2)(A)(iii), 355(j)(2)(C) (2012).

106. *Id.*

107. *Id.* § 355(b)(2); FDA, GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2) (draft) (Oct. 1999), <http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf> [<https://perma.cc/TS4B-RSJC>]; 21 C.F.R. § 314.54 (2016) (describing contents of a 505(b)(2) application). Like an ANDA, a 505(b)(2) application is subject to the Hatch–Waxman premarket patent litigation scheme. 21 U.S.C. § 355(c)(3) (2012).

108. Because a 505(b)(2) application contains original clinical data and generally does not lead to a substitutable product, some might be tempted to view the application as analogous to the new biosimilar application, particularly for purposes of understanding market penetration. Indeed, because FDA has approved some protein products under the drug provisions, the first follow-on version of a biotechnology-derived therapeutic protein product was, in fact, a 505(b)(2) product. The Omnitrope (somatropin recombinant) application cited FDA’s approval of Genotropin® (somatropin recombinant). Although the Omnitrope

neric drug company might use this option if patent considerations compelled it to propose a variation (such as a modification to the active ingredient or formulation) that required clinical testing and thus precluded an ANDA. A generic drug company might use this option to introduce a second-generation product that it believed would be more profitable than a strict copy. The hybrid approach—relying on the innovator’s data but proposing deliberate modifications—is not an option for biosimilar applicants.<sup>109</sup> Not only does the biologic statute lack a provision corresponding to section 505(b)(2), but it affirmatively states that a biosimilar applicant may not propose a “condition of use” that has not been approved for the reference product.<sup>110</sup> Thus, a second biologic applicant that wants to vary from or improve on a reference biological product must file a full application supported entirely by original research that it sponsored or has a right to reference.<sup>111</sup>

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experience may be instructive, caution is warranted before generalizing from products approved on the basis of 505(b)(2) applications—for two reasons:

*First*, although Omnitrope was found highly similar to its reference product, the standard of approval was safety and effectiveness. An applicant using the 505(b)(2) pathway is therefore not limited in the scope of approval; it may change the active ingredient, propose new uses, and develop new routes of administration. The scope of approval is limited only by the sponsor’s imagination, its research capabilities, and scientific possibilities. The biosimilar applicant, in contrast, is expected to duplicate the reference product, as closely as scientifically feasible, and approval is based on similarity.

*Second*, FDA’s interpretation and implementation of section 505(b)(2) has evolved and varied over the years, which would complicate aggregating data for analysis. For instance, Celgene’s application for Thalomid® was a 505(b)(2) application, not because it cited a previously approved application but because it was largely based on published literature. Pfizer used section 505(b)(2) for Zyrtec-D®, which combined cetirizine and pseudoephedrine, though it marketed the original Zyrtec®. Elan used section 505(b)(2) for Duraclon (clonidine hydrochloride), when it proposed a new dosage form (epidural administration) and formulation to treat cancer pain. *See generally* Letter from FDA to [Kathleen] M. Sanzo, Jeffrey B. Chasnow, Stephan E. Lawton, and William R. Rakoczy, Re: Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 (Oct. 14, 2003), <https://www.pharmamedtechbi.com/~media/Images/Publications/Archive/The%20Pink%20Sheet/65/042/00650420004/031020fda505b2response.pdf> [<https://perma.cc/J8M7-NXLG>]. While the market penetration of Omnitrope may be pertinent to the market penetration of biosimilars licensed under the BPCIA, the market penetration of other products with 505(b)(2) applications would be less instructive.

109. Congress considered and rejected language modeled on section 505(b)(2), for the biologic statute. H.R. 6257 § 3(a)(2), 109th Cong. (2006). For an additional perspective on this issue, see generally Janet Freilich, *Patent Infringement in the Context of Follow-On Biologics*, 16 STAN. TECH. L. REV. 9 (2012) (suggesting that biosimilar companies may be able to make manufacturing changes, formulation changes, and packaging changes to avoid innovator patents, but that FDA is likely to more tightly regulate cell culture conditions and purification, giving biosimilar applicants “less scope” to make changes that will bring them outside the range of equivalents for the innovator’s product).

110. 42 U.S.C. § 262(k)(2)(A)(i)(III) (2012).

111. If one applicant purchases a right to reference another applicant’s data, the resulting application is a full application not a biosimilar application. *Cf.* 21 C.F.R. § 314.3 (2016) (explaining right of reference for NDAs). It is theoretically possible that FDA will construe

Not only is the biologic statute less flexible than the drug statute, limiting biosimilar applicants to attempted duplicates, but FDA has apparently decided that the labeling of a biosimilar—the package insert with instructions for prescriber—should be virtually identical to the labeling of its reference product.<sup>112</sup> The agency has borrowed this approach from the generic framework; the drug statute requires generic drugs to have the same labeling as their reference products.<sup>113</sup> Although the biologic statute is silent, the comparative showing in a biosimilar application is analogous to the comparative showing in an ANDA; it is intended to justify the applicant's reliance on FDA's approval of the reference product.<sup>114</sup> Because the innovator's research proves the safety and effectiveness of the biosimilar product, the theory goes, biosimilar labeling should reflect the innovator's research, rather than the biosimilar applicant's research.<sup>115</sup>

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the biologic statute to permit *innovative* supplements to approved *biosimilar* applications, but this would probably be challenged in court. See Lietzan, *supra* note 9, at 152 n.206.

112. Although FDA had not issued a final decision on this issue when this Article was prepared, the agency had: (1) issued draft labeling guidance, (2) responded to three citizen petitions relating to labeling, and (3) approved the labeling for four biosimilar biologics. FDA, GUIDANCE FOR INDUSTRY: LABELING FOR BIOSIMILAR PRODUCTS (draft) (Mar. 2016) [hereinafter FDA DRAFT LABELING GUIDANCE]; Letter from FDA to Perry Siatis, Meredith Miller, William Chin, and Kay Holcombe, Re: Docket Nos. FDA-2015-P-2000, FDA-2015-P-4529, FDA-2015-P-5022 (July 12, 2016). These materials indicate that biosimilar labeling will include a statement that the product is a biosimilar and will explain the concept of biosimilarity, but will otherwise generally adopt the text of the reference product labeling word for word, changing product names where appropriate. For instance, § 14.1 of the Neupogen labeling begins with an Amgen study assessing the “safety and efficacy of NEUPOGEN to decrease the incidence of infection.” AMGEN, NEUPOGEN® PRESCRIBING INFORMATION § 14.1 (2016), [http://pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/neupogen/neupogen\\_pi\\_hcp\\_english.ashx](http://pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/neupogen/neupogen_pi_hcp_english.ashx) [<https://perma.cc/XN3W-WF9U>]. The same section of the Zarxio labeling begins with the same study and same sentence, but it refers to the “safety and efficacy of *filgrastim* to decrease the incidence of infection.” ZARXIO PRESCRIBING INFORMATION § 14.1 (2016) (emphasis added), <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=fe707775-a0ae-41b5-a744-28c41889fce8&type=display> [<https://perma.cc/MH7R-8AL8>].

113. 21 U.S.C. § 355(j)(2)(A)(v) (2012). The drug statute allows differences due to permitted deviations in the generic drug's route of administration, dosage form, strength, or active ingredient (in a combination product), or because the drugs are produced or distributed by different manufacturers. *Id.* It also implicitly permits the generic applicant to omit indications claimed by patent. *Id.* § 355(j)(2)(A)(viii).

114. FDA DRAFT LABELING GUIDANCE, *supra* note 112, at 3.

115. Despite use of generic-style labeling, biosimilar applicants may be treated like drug innovators—rather than like generic drug applicants—in product liability litigation. That is, they may not benefit from preemption the way that generic drug companies do, for the following reason. As a general rule, labeling must be revised promptly to include new warnings. 21 C.F.R. § 201.57(c)(6)(i) (2017). FDA's regulation governing changes to approved drugs permits this type of labeling change to be made unilaterally and described in a supplement that FDA reviews after the fact. 21 C.F.R. § 314.70(c)(6)(iii) (2012). Although this regulation applies to generic drugs, the portion permitting unilateral safety-related labeling changes does not apply. 21 C.F.R. § 314.97 (2008); Brief for the United States as Amicus Curiae Supporting Respondents at 25, *Pliva v. Mensing*, Nos. 09-993, 09-1039, 109-

In the absence of automatic substitution, biosimilar applicants plan to promote their products.<sup>116</sup> But the preceding paragraphs suggest their promotional strategies will need to be different from innovator promotional strategies. The challenge lies in promoting a product against its competition in the absence of clinically meaningful differences between the products. At most, a biosimilar applicant will have minor distinctions to point out. Because a biosimilar applicant need not seek approval for all reference product indications, routes of administration, dosage forms, and strengths, biosimilars to the same reference product may differ from each other with respect to scope of approval.<sup>117</sup> There may also be differences in formulation and delivery device from other biosimilars and even the reference product, which could be described.<sup>118</sup> The biosimilar applicant will not be able to suggest clinically meaningful differences between its product and the reference product, however, as this would be inconsistent with the standard of approval itself.<sup>119</sup> Further, FDA's decision that biosimilar labeling should generally copy the reference product label-

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1501. A state law claim against an innovator alleging inadequate warnings in its package insert is generally not preempted by federal law (FDA's approval of the labeling in question) because the innovator has both the obligation and the legal authority to revise its labeling unilaterally to reflect new safety information. *Wyeth v. Levine*, 555 U.S. 555 (2009). Such a claim is generally preempted when brought against a generic company, however, because the drug statute requires a generic drug's labeling to be the same as the labeling of its reference drug and FDA does not permit generic companies to make unilateral changes to their labeling. *Pliva v. Mensing*, 564 U.S. 604, 613-23 (2011). The biologic statute does not require a biosimilar biologic's labeling to be the same as the labeling of its reference product, nor has FDA published a regulation to that effect. This eliminates most of the *Pliva* rationale for finding preemption. But the agency has apparently required the labeling to be essentially the same, and it is not clear whether biosimilar applicants will be allowed to make unilateral safety-related labeling changes. FDA has said that the regulation governing changes to approved biologics applies to biosimilars, but it may take the view that unilateral safety-related changes are not appropriate. 21 C.F.R. § 601.12 (2016); FDA DRAFT LABELING GUIDANCE, *supra* note 112, at 5. If FDA decides to permit these changes, the *Pliva* case would clearly not apply, and there would be no preemption.

116. *E.g.*, Jaimy Lee, *Sandoz: Zarxio Marketing to Be Similar to a Branded-Drug Launch*, MM&M (Sept. 3, 2015), <http://www.mmm-online.com/campaigns/sandoz-zarxio-marketing-to-be-similar-to-a-branded-drug-launch/article/436778/> [<https://perma.cc/7GWF-K44T>] ("The approach for marketing biosimilars is much closer to the approach for a branded product than that of generic medicine, and as such Sandoz has a fully integrated commercial organization behind the launch of Zarxio." (quoting Leslie Pott, Vice President of Communications for Sandoz)).

117. FDA Q&A GUIDANCE, *supra* note 68, at 7, 12. Nor is a biosimilar applicant required to seek approval of every reference product presentation. *Id.* at 7. For instance, Neupogen is available in both vials and pre-filled syringes, but Sandoz sought approval of Zarxio only in pre-filled syringes. Sue Sutter, *Biosimilar but Different: Zarxio, Neupogen Diverge on Syringes, Vials*, PINK SHEET (Mar. 16, 2015), <https://pink.pharmaintelligence.informa.com/PS056727/Biosimilar-But-Different-emZarxioem-emNeupogenem-Diverge-On-Syringes-Vials> [<https://perma.cc/7LPQ-BERZ>].

118. FDA Q&A GUIDANCE, *supra* note 68, at 6-7.

119. 42 U.S.C. § 262(i) (2012) (defining biosimilar).

ing—and therefore describe the innovator’s studies—may further limit the biosimilar applicant’s promotional options. The agency’s regulations require that prescription drug promotional materials be consistent with the applicable package insert,<sup>120</sup> which may preclude promotion on the basis of data described only in the biosimilar application. The biosimilar industry has pressed FDA to “find a way” for biosimilar applicants to promote their products on the basis of their own trials,<sup>121</sup> and recent developments in First Amendment jurisprudence may give some of them resolve to make these off-label claims despite agency rules.<sup>122</sup> Individual firms may vary in their willingness to test the boundaries of the First Amendment, however, and promotional strategies may vary and evolve.

(b) *Financial Considerations*

Traditional innovator-style advertising and promotion, focusing on product features and clinical differences, are unlikely to drive biosimilar market penetration. What remains, for the most part, may be price competition and the related considerations of coverage and reimbursement. Put another way, the statute’s approach of forcing duplication—the lack of a suitability petition option or hybrid application pathway—may be central to ensuring robust price competition. That said, the high cost associated today with developing and launching a biosimilar may mean that discounts are modest in the early years.<sup>123</sup> The small number of biosimilar applications for each reference product could have the same effect, limiting the price competition and discounting in the early years. If the premarket burden and risk vary by product type, discounts may vary, and market penetration could vary correspondingly. And as the burden and risk decline

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120. 21 C.F.R. § 201.100(d)(2) (2017).

121. Sue Sutter, *Biosimilars’ Generic-Style Labeling Limits Data Promotion, Companies Say*, PINK SHEET (May 25, 2015, 12:01 AM), <https://pink.pharmamedtechbi.com/PS056882/Biosimilars-Genericstyle-Labeling-Limits-Data-Promotion-Companies-Say> [<https://perma.cc/765N-5E89>] (noting that Hospira and Amgen argue that “being able to discuss the data underlying approved biosimilars will be critical to building public support for the products”).

122. See, e.g., *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012) (vacating misbranding conviction of a pharmaceutical sales representative that was based on his having promoted Xyrem® (sodium oxybate) for unapproved uses using speech that was truthful and non-misleading); *Amarin v. FDA*, 106 F. Supp. 3d 196 (D.D.C. 2015) (finding manufacturer likely to succeed on the merits of argument that FDA’s threat to bring misbranding action for truthful statements promoting Vascepa® (icosapent ethyl) for an unapproved use impermissible burdens its First Amendment rights).

123. E.g., Ben Hirschler, *Novartis Launches First U.S. ‘Biosimilar’ Drug at 15 Percent Discount*, REUTERS (Sept. 3, 2015, 8:13 AM), <http://www.reuters.com/article/us-novartis-drug-idUSKCNOR30C220150903> [<https://perma.cc/68BH-9RNL>]; Nicholas Florke, *Remicade Biosimilar to Launch in November, 15% Cheaper Than Innovator*, INSIDEHEALTHPOLICY (Oct. 17, 2016).



over time, discounting and therefore market penetration could increase.

Coverage and reimbursement for biologics and biosimilars is complex and evolving, making it difficult to offer anything more than initial impressions about their influence on market penetration. But several points stand out. *First*, adoption of “specialty pharmacy” arrangements may be a way for payers to invoke traditional cost containment strategies, driving market penetration of biosimilars. *Second*, these arrangements are complex and involve parties with misaligned interests, which may lead to practices that might otherwise attract criticism—like distribution restrictions and price increases—but that in this context, counterintuitively achieve cost savings for the healthcare system. *Third*, under the federal Medicare program, at least for physician-administered products, it may be impossible for biosimilar applicants to compete with each other on any basis, *including* price.

Generally speaking, a patient’s prescription medicine is covered under either her medical benefit or her pharmacy benefit.<sup>124</sup> Typically, when a medicine is self-administered, it is dispensed by a pharmacy and covered under the pharmacy benefit.<sup>125</sup> When it is administered in a physician’s office or other outpatient facility, it is ordinarily covered instead under the medical benefit.<sup>126</sup> Biologics tend to be administered by physicians and, thus, are more likely to be covered by the medical benefit. The emergence of “specialty pharmacies,” however, along with creative dispensing practices, may make it possible for payers to move biologics to the pharmacy benefit.

The phrase “specialty pharmaceutical” (or “specialty medicine”) has no legal significance, but various entities in the healthcare delivery and finance systems—manufacturers, insurance companies, pharmacies, and providers—use it to describe medicines that share certain characteristics and that they handle or manage differently from others.<sup>127</sup> Specialty medicines are typically complex products,

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124. See, e.g., ROBERT NAVARRO & RUSTY HAILEY, *Overview of Prescription Drug Benefits in Managed Care*, in *MANAGED CARE PHARMACY PRACTICE* 17, 20 (2009). Medicines administered in the inpatient setting, for instance in connection with surgery, are usually reimbursed as part of the medical procedure in question.

125. *Id.*

126. *Id.*

127. For representative definitions, see *Specialty Pharmaceuticals: Facts and Figures*, PHARMACEUTICAL COMMERCE (Dec. 27, 2012), <http://pharmaceuticalcommerce.com/special-report/specialty-pharmaceuticals-facts-and-figures/> [https://perma.cc/3YLE-5K5N]; ACAD. OF MANAGED CARE PHARMACY, *THE AMCP FORMAT FOR FORMULARY SUBMISSIONS VERSION 3.1* 20 (2012); Adam J. Fein, *Defining Specialty Pharmacy*, *DRUG CHANNELS* (Feb. 5, 2013), <http://www.drugchannels.net/2013/02/defining-specialty-pharmacy.html> [https://perma.cc/4DA7-7X4V]; Ian Spatz & Nancy McGee, *Specialty Pharmaceuticals*, *HEALTHAFF.* (Nov. 25,

often biotechnology-derived and difficult to manufacture. They may require temperature-controlled (cold-chain) shipping and storage, and they may require special handling until the moment of administration. Most are for serious or chronic conditions, many are difficult to administer, and many have complex side effect profiles. They might require prescriber, pharmacist, or patient education and continual patient monitoring. Many are subject to use or distribution restrictions imposed by FDA.<sup>128</sup> Others are subject to distribution restrictions adopted voluntarily by their manufacturers due to the need for cold-chain shipping, perhaps, or in order to reduce the risk of counterfeiting.<sup>129</sup>

Some physician-administered biologics may be shifted to the pharmacy benefit through use of specialty medicine distributing and dispensing arrangements. In this scenario, the biologic is “dispensed” by a “specialty pharmacy” for subsequent physician administration.<sup>130</sup>

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2013), [http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief\\_id=103](http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=103) [<https://perma.cc/7C55-T7UY>]; Robert C. McDonald, *Managing the Intersection of Medical and Pharmacy Benefits*, 14 SUPPLEMENT TO J. MANAGED CARE PHARMACY 4, S8 (May 2008), [http://www.amcp.org/data/jmcp/JMCPSupp\\_S7-S11.pdf](http://www.amcp.org/data/jmcp/JMCPSupp_S7-S11.pdf) [<https://perma.cc/QQW3-RRE2>]; Jack McCain, *Connecting Patients with Specialty Products: Distribution Models for Biologics and Other Specialty Pharmaceutical Products*, 9 BIOTECH. HEALTHCARE 8 (2012), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411231/pdf/bh0902008.pdf> [hereinafter McCain, *Distribution Models for Biologics and Other Specialty Pharmaceutical Products*]; Jack McCain, *Connecting Patients with Specialty Products: The Future of Specialty Drug Distribution*, 9 BIOTECH. HEALTHCARE 13 (2012), <https://www.ncbi.nlm.nih.gov/pubmed/23091429> [<https://perma.cc/AWJ7-D3QE>] [hereinafter McCain, *The Future of Specialty Drug Distribution*].

128. For instance, Tysabri® (natalizumab) is often considered a specialty pharmaceutical. Tysabri is approved for treatment of multiple sclerosis but increases the risk of progressive multifocal leukoencephalopathy, an opportunistic viral infection of the brain that usually leads to death or severe disability. One’s risk increases with longer treatment duration, prior immunosuppressant use, and the presence of certain antibodies. FDA has required the sponsor to adopt a Risk Evaluation and Mitigation Strategy (REMS) that permits dispensing only by specially certified pharmacies and infusion sites. See REMS: BLA 125104, <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=63> [<https://perma.cc/CFW7-C9JY>]; see also 21 U.S.C. § 355-1 (2012) (authorizing FDA to impose REMS).

129. FDA may only require six types of restriction in a REMS: special training or credentials for prescribers, special certification for pharmacies, restricted dispensing locations, laboratory or related testing of patients, patient monitoring, and patient registries. 21 U.S.C. § 355-1(f)(3) (2007-08). Genentech has placed non-REMS restrictions on Avastin (bevacizumab) due to concerns about counterfeiting. Physician offices may obtain the biologic from only a few specialty distributors, and hospitals may obtain it from only a few wholesalers. The distributors and wholesalers have agreed not to distribute further to secondary wholesalers. See McCain, *The Future of Specialty Drug Distribution*, *supra* note 127.

130. Specialty pharmacies often have specialized storage and handling capabilities and expertise, as well as familiarity with distribution restrictions. They sometimes offer special programs and support for patients with chronic or rare conditions, perhaps partnering with treatment providers in an effort to improve outcomes; they might offer, for example, packaging that promotes adherence to therapy and frequent personalized contact with the patients. *E.g.*, ACAD. OF MANAGED CARE PHARMACY, *supra* note 127, at 35.

Procedures known in the industry as “white bagging” and “brown bagging” physically transfer the dispensed medicine from the specialty pharmacy to the relevant physician’s office or outpatient facility.<sup>131</sup> This medicine would be reimbursed under the patient’s pharmacy benefit. Use of the pharmacy benefit in turn facilitates use of conventional cost-management tools, such as formulary management, prior authorization requirements, and copayments (fixed amounts) or coinsurance (percentages).<sup>132</sup> When FDA approved Zarxio, the largest pharmacy benefit manager (PBM) in the country pushed its clients (payers) to adopt a specialty pharmacy arrangement for both Neupogen and Zarxio.<sup>133</sup> This permitted reimbursement through the pharmacy benefit and allowed the PBM to use prior authorization and formulary exclusion to promote use of Zarxio instead of Neupogen.<sup>134</sup> The “specialty pharmacy” concept is gaining a foothold in the healthcare finance and delivery system and has the potential to drive biosimilar market penetration by facilitating adoption of pharmacy benefit cost-management tools.

Specialty pharmacy is an evolving and complicated area, however, involving healthcare delivery and finance system stakeholders that may have unexpected or conflicting interests or that may make decisions that seem counter-intuitive. Here is an example of conflicting interests: a payer urging the specialty pharmacy arrangement to achieve cost savings might face opposition from larger physician offices, which may prefer that specialty medicines remain on the medical benefit, which provides them with more revenue.<sup>135</sup> White and

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131. White bagging generally involves dispensing by a pharmacy and shipment to the provider in time for treatment. Brown bagging generally involves dispensing by a pharmacy directly to the patient, who brings it to the physician’s office at the time of treatment. See generally McCain, *Distribution Models for Biologics and Other Specialty Pharmaceutical Products*, *supra* note 127.

132. See PHARM. STRATEGIES GROUP, UNDERSTANDING SPECIALTY PHARMACY MANAGEMENT AND COST CONTROL 6-7 (2010).

133. A pharmacy benefit manager administers pharmacy benefit programs, typically for the entities that ultimately pay for the medicines (e.g., insurance companies or corporations). Among other things, a pharmacy benefit manager assists with the plan design, develops and maintains the formulary, negotiates with pharmacies and manufacturers, and processes claims. Essentially, a pharmacy benefit manager acts as an intermediary between the payer and everyone else in the healthcare system. See generally Joanna Shepherd, *The Fox Guarding the Henhouse: The Regulation of Pharmacy Benefit Managers by a Market Adversary*, 9 N.W. J.L. & SOC. POL’Y 1, 2-4 (2013).

134. See Cathy Kelly, *PBM Wants Filgrastim in Pharmacy Benefit to Push Biosimilar Use*, PINK SHEET (Mar. 16, 2015), <https://pink.pharmaintelligence.informa.com/PS056713/PBM-Wants-Filgrastim-In-Pharmacy-Benefit-To-Push-Biosimilar-Use> [<https://perma.cc/EY2F-ZK9T>].

135. The leverage of any particular physician office may depend on the medicine, the alternatives in the class, and the office’s specialty. Brand-loyalty, which varies by physician specialty, could also prompt physicians to push back on—or ignore—particular cost-management strategies. Allergists are thought to be more price-sensitive, for example, and

brown bagging for the pharmacy benefit denies physicians the payment they would otherwise receive under the medical benefit as a result of the “buy and bill” approach.<sup>136</sup> Physicians in smaller practices may prefer white and brown bagging for the pharmacy benefit, however, because it reduces their financial risk.<sup>137</sup>

Two further examples illustrate unexpected decisions with counter-intuitive cost-saving outcomes. *First*, after moving an expensive specialty medicine to the pharmacy benefit, a payer—that is, neither FDA nor the innovator—might impose distribution restrictions, limiting the supply chain to both specialty pharmacies and specialty distributors. These restrictions may increase cost savings for the healthcare finance system because limiting the number of pharmacies that may distribute (and thus purchase) a medicine allows the payer to consolidate its purchasing power.<sup>138</sup> *Second*, price increases may actually increase cost savings for the healthcare finance system: Sandoz found that specialty pharmacy arrangements forced it to *increase* the price of its follow-on protein product, Omnitrope®, in order to achieve market penetration.<sup>139</sup> Distribution restrictions and price increases, sometimes reflexively assumed to be harmful, may actually turn out to be a path to cost savings.

The rules governing coverage and reimbursement of biosimilar biologics under government health insurance programs are different. The Medicare program, which will be particularly relevant for biologics that are heavily prescribed to older populations, has a different incentive structure. To begin with, the Medicare Part B reimburse-

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rheumatologists demonstrate greater levels of brand loyalty. See Henry Grabowski et al., *Biosimilars*, in ENCYC. OF HEALTH ECON. 86, 92-93 (2016); see also Sue Sutter, *Biosimilar Prescribing Decisions May Depend Upon Disease State*, PINK SHEET (Oct. 24, 2016), <https://pink.pharmamedtechbi.com/PS119377/cBiosimilar-Prescribing-Decisions-May-Depend-Upon-Disease-State> [<https://perma.cc/SHD7-JDBH>] (quoting official from Express Scripts Holding Co. for proposition that physicians may be more likely to prescribe a biosimilar for inflammatory conditions than for cancer).

136. Under the “buy and bill” approach, the physician purchases the drugs, manages an inventory, administers the drugs, and submits claims. See Tim Casey, *Alternative Distribution Strategies: “Buy and Bill” and “White Bagging”*, FIRST REPORT: MANAGED CARE (Jan. 21, 2014). In addition to more revenue, the buy and bill approach may make it easier to change medications and adjust dosing regimens.

137. *Id.*

138. See NAVARRO & HAILEY, *supra* note 124, at 32; Ian Spatz & Nancy McGee, *supra* note 127, at 1, 3.

139. See Sue Sutter, *Biosimilar Pricing: Sandoz Vows Not to Make Omnitrope ‘Mistake’ with Filgrastim*, PINK SHEET (Dec. 22, 2014), <https://pink.pharmamedtechbi.com/PS056542/Biosimilar-Pricing-Sandoz-Vows-Not-To-Make-emOmnitropeem-Mistake-With-Filgrastim> [<https://perma.cc/GQ55-KE43>] (quoting Sandoz executive that the company sold Omnitrope through specialty pharmacies and “because they make a profit based on a percentage of the sales price of the drug, we had a lousy experience in selling the product *because we priced it too low, and we had to increase the price to sell the product*” (emphasis added)).

ment rules may remove any incentive for a prescriber administering a biologic in an outpatient setting to select the reference product instead of the biosimilar.<sup>140</sup> Under Part B, a provider generally pays for medicine and then seeks reimbursement from patient insurance. Reimbursement is typically 106% of the manufacturer's average sales price (ASP).<sup>141</sup> The 6% add-on is viewed as payment for the provider's resource costs and overhead. In 2010, Congress specified that Part B reimbursement for a biosimilar should be 100% of the biosimilar's ASP plus 6% of the reference product's ASP. In other words, the 6% add-on, the payment to the provider for services and overhead, must be the same for the biosimilar product and the reference product.<sup>142</sup> This was intended to eliminate the financial incentive to prescribe the product with the higher ASP, typically the reference product.<sup>143</sup>

In addition, Medicare will provide the same amount in reimbursement for every biosimilar to the same reference product. This same-amount rule results from a decision relating to the codes assigned to biosimilars for reimbursement purposes. Items and services provided in the delivery of healthcare are assigned "Healthcare Common Procedure Coding System" codes, or HCPCS codes. Most drugs receive a "J-code," and an innovative drug without any generic equivalents generally receives a unique J-code. Once generic copies of that drug are approved, however, the generics and reference product are grouped together. A provider receives the same amount in reimbursement under Part B for each drug in the same J-code: the volume weighted average ASP for the code plus 6%.<sup>144</sup> This grouping and formula provide an incentive for providers to use the generic drug,

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140. Medicare Part B generally covers services received in an outpatient clinical or hospital outpatient setting, as well as the medicines involved. Inpatient services, and the medicines involved, are usually covered under Part A. *See generally* PATRICIA A. DAVIS ET AL., CONG. RESEARCH SERV., R40425, MEDICARE PRIMER (Sept. 2014).

141. Because of sequestration (federal spending cuts scheduled to be in effect through 2021), at the time of writing Medicare reimbursement was actually at ASP plus 4.3%. *See* Alex Brill & Brett Leitner, *Sequestration's Uniform Medicare Cut Will Yield Disparate Impacts Across Providers*, HEALTH LAW. (June 11, 2013), <http://www.aei.org/publication/sequestrations-uniform-medicare-cut-will-yield-disparate-impacts-across-providers/> [<https://perma.cc/E6DU-QF73>].

142. The Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 3139, 124 Stat. 439-40 (2010); 42 U.S.C. § 1395w-3a(b)(8) (2012).

143. *See* Anna Kraus, Esther Scherb & Stefanie Doebler, *CMS Releases New Reimbursement Guidance for Biosimilars*, NAT'L L. REV. (Apr. 7, 2015), <https://www.natlawreview.com/article/cms-releases-new-reimbursement-guidance-biosimilars> [<https://perma.cc/E3TV-MXXT>]; *see also* MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: IMPROVING INCENTIVES IN THE MEDICARE PROGRAM 124-30 (2009).

144. OFFICE OF THE INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVS., MEDICARE PAYMENTS FOR NEWLY AVAILABLE GENERIC DRUGS 2-3 (2015).

assuming its acquisition costs are lower.<sup>145</sup> Because a biosimilar biologic is not analogous to a generic drug, however, CMS is not placing biosimilars in the same J-code as their reference products. That said, all of the products biosimilar to a particular reference product will be placed together within the same J-code. In other words, the reference product will have one J-code, and its biosimilars will be lumped together in a separate J-code. CMS also intends to use a single ASP for all biosimilars lumped together in one code.<sup>146</sup> The bottom line is that under current policy, Medicare reimburses all biosimilars to the same reference product equally, even if those biosimilars are not approved for the same indications or differ in other ways, and even if their acquisition costs for providers are different. This will make it difficult, if not impossible, for biosimilar applicants to differentiate their products in the marketplace.

Some biosimilars will be covered instead under Medicare Part D, which provides insurance coverage for biologics that do not meet the Part B coverage criteria and are generally dispensed by pharmacies. Part D is administered by private companies (Part D sponsors) subject to CMS oversight, including oversight with respect to formulary review and management. Part D sponsors may add biosimilars to their formularies at any time, and removal of the corresponding reference product will be permitted on a case-by-case basis if the revised formulary continues to meet CMS standards.<sup>147</sup> In the Part D scheme, biosimilars are both like and unlike innovative products. For instance, each therapeutic category and class of Part D drugs must contain at least two drugs “that are not therapeutically equivalent and bioequivalent.”<sup>148</sup> This precludes a category and class from comprising only an innovative drug and its generic equivalents. CMS is treating biosimilars like generic drugs for purposes of this requirement, even though a biosimilar is not “therapeutically equivalent”

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145. Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 538 (2011).

146. Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B for CY 2016, 80 Fed. Reg. 70,886, 71,100-01 (Nov. 16, 2015) (to be codified at 42 CFR pts. 405, 410, 411, et al.) (final rule for physician fee schedule for CY 2016). In July 2017, CMS solicited comments on the new payment policy and signaled that it might now be open to individual J-codes for biosimilars. Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B for CY 2018; Medicare Shared Savings Program Requirements; and Medicare Diabetes Prevention Program, 82 Fed. Reg. 33,950 (July 21, 2017) (to be codified at 42 C.F.R. pts. 405, 410, 414, 424, and 425).

147. Memorandum from CMS on the Part D Requirements for Biosimilar Follow-On Biological Products to Part D Sponsors (Mar. 30, 2015) [hereinafter Part D Guidance] (citing Medicare Prescription Drug Benefit Manual, ch. 6, § 30.1.5). The Part D Guidance does not apply to interchangeable biologics, which presumably the agency will address at a later date.

148. 42 C.F.R. § 423.120(b)(2) (2016).

and “bioequivalent” to its reference product. Thus, it is not sufficient simply to make a reference product and its biosimilar available.<sup>149</sup> At the same time, according to CMS, biosimilars should be treated like innovative products for reimbursement purposes.<sup>150</sup> Thus, for instance, a subscriber with a low-income subsidy will be responsible for the copayment associated with innovative products, which is higher than a generic copayment. But unlike innovative products, biosimilars are not subject to the requirement of a manufacturer discount while beneficiaries are in the Part D coverage gap.<sup>151</sup> This could make the biosimilar more expensive for patients than its reference product, affecting patient willingness to remain on the biosimilar while in the gap.<sup>152</sup>

State Medicaid plans are likely to employ many of the same cost management techniques as Medicare Part D sponsors and private health plans in order to further biosimilar adoption. All states currently elect to include prescription drug benefits as part of their Medicaid benefit packages.<sup>153</sup> Like other payer plans, state Medicaid plans include formularies, set and managed by formulary committees, which take into account many of the same considerations as other formulary committees. Following approval of the first biosimilar, CMS issued guidance to the states describing the launch of biosimilar products as “a unique opportunity to achieve measurable cost savings and greater beneficiary access to expensive therapeutic treatments for chronic conditions.”<sup>154</sup> It recommended that states use

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149. Part D Guidance, *supra* note 147.

150. *Id.* (a “generic drug” is a drug for which an application under section 505(j) of the FDCA has been approved (citing 42 C.F.R. § 423.4 (2015)); 42 U.S.C. § 1396r-8(k)(7)(A)(i) (2012) (a multiple-source or multi-source drug is a drug for which there are approved therapeutic equivalents)).

151. The Medicare Part D benefit has a “coverage gap” during which beneficiaries are entirely responsible for the cost of their prescription drugs. In 2010, Congress created a Coverage Gap Discount Program to help close the gap. The Patient Protection and Affordable Care Act of 2010 § 3301, Pub. L. No. 111-148, 124 Stat. 119 (2010); Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, §1101, 124 Stat. 1029 (2010).

152. See Cathy Kelly, *Biosimilar Costs Could Exceed Brands in Part D Coverage Gap*, PINK SHEET DAILY (Apr. 7, 2015), <https://pink.pharmamedtechbi.com/PS078446/Biosimilar-Costs-Could-Exceed-Brands-In-Part-D-Coverage-Gap> [<https://perma.cc/9THH-TN4L>].

153. OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH & HUMAN SERVS., MEDICAID REBATES FOR PHYSICIAN-ADMINISTERED DRUGS (2004), <https://oig.hhs.gov/oei/reports/oei-03-02-00660.pdf> [<https://perma.cc/CD27-RWYB>]; OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH & HUMAN SERVS., STATES’ COLLECTION OF MEDICAID REBATES FOR PHYSICIAN-ADMINISTERED DRUGS (2011), <https://oig.hhs.gov/oei/reports/oei-03-09-00410.pdf> [<https://perma.cc/R7SD-YD7Z>].

154. CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP’T OF HEALTH & HUMAN SERVS., MEDICAID DRUG REBATE PROGRAM NOTICE RELEASE NO. 92: BIOSIMILARS AND THE MEDICAID DRUG REBATE PROGRAM (2015). Because the federal government pays states a percentage of their program expenditures, the federal government has an interest in mechanisms that reduce costs for covered medicines. In order for federal funds to be provided for

available cost-management tools (such as prior authorization requirements and preferred drug lists) to steer patients towards biosimilars.<sup>155</sup> CMS also pointed out that “reminding” physicians how to prescribe biosimilars, because they are not substitutable, “is important to encourage and maximize their use.”<sup>156</sup>

(c) *Other Factors—Immunogenicity and Naming*

Although financial considerations are likely to be paramount, concerns about immunogenicity might affect decisions made by formularies, physicians, and other decision-makers and therefore affect market penetration. FDA has raised the concern that switching between biologics made by different companies might exacerbate or change immunogenic responses to one or the other.<sup>157</sup> An interchangeability determination requires studies addressing this very question. In the absence of those studies, some may choose biosimilars for treatment-naïve patients (where no switch of proteins is involved) but not for established patients (where a switch would be necessary).<sup>158</sup> If a biosimilar applicant includes a cross-over from the reference product to the biosimilar in one of its clinical trials for initial biosimilar licensure,<sup>159</sup> the resulting data may persuade some de-

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its outpatient drugs, the manufacturer must have entered into an agreement to pay rebates to the states. See 42 U.S.C. § 1396r-8(a) (2012).

155. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 154, at 2. Subject to some exceptions, however, if the manufacturer has signed the National Rebate Agreement, the state plan must permit coverage of a drug excluded from the formulary, through a prior authorization program. 42 U.S.C. § 1396r-8(d)(4)(E) (2012). That is, exclusion from the formulary does not lead to lack of coverage.

156. CTRS. FOR MEDICARE & MEDICAID SERVS., *supra* note 154, at 2.

157. *E.g., Biosimilars Implementation: Hearing on the BPCI Act Before the S. Subcomm. on Primary Health & Retirement Sec.*, 114th Cong. (Sep. 17, 2015) [hereinafter *Biosimilars Implementation Hearing*] (statement of Dr. Woodcock, Director, Center for Drug Evaluation and Research) (“The question is would [continued switching] cause additional harm because of unexpected immune responses. Because unlike most of our small molecule drugs, the body recognizes these large protein molecules that are biosimilars and often, will make, in some people, will make an immune response. And what the concern has been is that this continued switching could raise that immunity—sort of provide a booster effect and cause untoward effects.”).

158. TUFTS CTR., *supra* note 49, at 3-4 (noting that “one-third of physicians surveyed said they would be unlikely to switch an existing patient from an originator biologic to a biosimilar,” and although “[a]ll payers said they would recommend use of biosimilars for new patients” only “75% of payer respondents said they would likely recommend therapeutic switching of biosimilars”).

159. For instance, Amgen’s application for Amjevita included data from a subset of subjects with plaque psoriasis who underwent a single transition from Humira to Amjevita at week 16. These subjects were compared with subjects who had been randomized to Humira in the first instance and remained on Humira after week 16. Amgen explained in its briefing materials that the purpose of the analysis was to “establish safety, efficacy, and immunogenicity following a single physician-supervised transition” from Humira to Amjevita. AMGEN, BIOLOGICS LICENSE APPLICATION FOR ABP 501 13 (2016). See Amgen,



cisionmakers to switch established patients to the biosimilar in question.<sup>160</sup> Others may wait for observational data from therapeutic interchange. Still others may wait until FDA starts to grant interchangeability determinations, and others might wait for an interchangeability determination for the product in question. The impact of unanswered immunogenicity questions on the market uptake of any particular biosimilar may depend in part on whether its primary uses are acute, short-term, or chronic conditions (because a product for chronic conditions raises the switching issue), the sensitivity of the particular patient population to immunogenic reactions,<sup>161</sup> and how many new (naïve) patients are diagnosed each year.

FTC staff have also argued that FDA's decision to give biologics distinctive nonproprietary names will affect biosimilar market penetration.<sup>162</sup> In colloquial terms, the nonproprietary name is the lower-case word that appears in parenthesis after the brand name: inflix-

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Comment Letter on the Transparent Labeling of Biosimilars 4 (July 20, 2015) (“Parallel-arm clinical studies that have a single transition from the reference product to the biosimilar candidate are being conducted by some biosimilar manufacturers.”).

160. The Executive Director for Scientific Affairs at Sandoz, which is developing biosimilars, has explained that single switch data are valuable because of the “reassurance” they provide to patients about the idea of switching from the reference product to the biosimilar. Sue Sutter, *Biosimilar Interchangeability: NOR-SWITCH-Type Study Not Enough for US FDA*, PINK SHEET (Nov. 1, 2016), <https://pink.pharmamedtechbi.com/PS119433/Biosimilar-Interchangeability-NORSWITCHType-Study-Not-Enough-For-US-FDA> [<https://perma.cc/3XJV-VZ5U>]. The results of the crossover should be publicly available even though not included in the package insert. The company may announce them at professional conferences and in press releases; it could publish them in a scientific journal; the data may be discussed at the advisory committee meeting considering the biosimilar application; and FDA's website must include the memoranda prepared by the agency reviewers. See 21 U.S.C. § 355(l) (2012). Cf. FDA, CROSS-DISCIPLINE TEAM LEADER REVIEW: BLA 125544, at 26-27 (Apr. 5, 2016), [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/125544Orig1s000CrossR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125544Orig1s000CrossR.pdf) [<https://perma.cc/7CD7-3ZCW>] (“Further, because the objectives of a 351(k) application are to establish biosimilarity and not to independently establish safety [or] effectiveness of the product, inclusion in the proposed labeling of the [REDACTED] is not warranted and will not be included. Of note, these product-specific data for [Inflixtra] were presented at the Arthritis Advisory Committee on February 9, 2016 and FDA's review of these data will be publicly available after licensure as part of the FDA ‘action package’ for the public to review.”).

161. Patient-specific factors that can affect immunogenic response include concomitant medications, general immunologic status, age, prior exposure to the protein or structurally similar proteins, and genetic factors. FDA IMMUNOGENICITY GUIDANCE, *supra* note 25, at 9-12.

162. Federal Trade Commission, Comment Letter on the Nonproprietary Naming of Biological Products 2 (Oct. 27, 2015), [https://www.ftc.gov/system/files/documents/advocacy\\_documents/ftc-staff-comment-submitted-food-drug-administration-response-fdas-request-comments-its-guidance/151028fdabiosimilar.pdf](https://www.ftc.gov/system/files/documents/advocacy_documents/ftc-staff-comment-submitted-food-drug-administration-response-fdas-request-comments-its-guidance/151028fdabiosimilar.pdf) [<https://perma.cc/4TSN-3K4R>] (arguing that the proposal could “result in physicians incorrectly believing that biosimilars’ drug substances differ in clinically meaningful ways” and thereby “deter physicians from prescribing biosimilars, thus impeding the development of biosimilar markets and competition”).

mab for Remicade, to give an example, and fluoxetine for Prozac.<sup>163</sup> FDA has proposed that all biologics, including innovative products, have distinct nonproprietary names, to ensure identification and accurate attribution of emerging safety signals.<sup>164</sup> Rapid and accurate attribution of adverse events is thought essential given the risk of immunogenicity and the possibility that either: (1) differences between the reference product and biosimilar may not emerge during premarket testing due to the rareness or latency period of the immunogenic reaction in question, or (2) one or the other company may make a manufacturing change that unexpectedly triggers an immune reaction.<sup>165</sup> Thus, every biological product will have a nonproprietary name that includes a suffix comprising four lowercase letters.<sup>166</sup> Alt-

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163. The nonproprietary name is also called the “established name” or, in the case of a biologic, the “proper name.” See 21 U.S.C. § 352(e) (2012); 42 U.S.C. § 262(a)(1) (2012); 21 C.F.R. § 610.62 (2016). The FDCA requires use of the nonproprietary name in drug labels and labeling, and since the late 1960s, FDA has accepted use of the “United States Adopted Name” (USAN) adopted by the USAN Council, a private group that includes members from FDA, the American Medical Association, and the United States Pharmacopoeia. See USAN HANDBOOK 12 (5th ed. 1999); Designated Names; Revocation of List of Official Names of Drugs, 49 Fed. Reg. 37,574 (Sept. 25, 1984) (to be codified at 21 C.F.R. pt. 299). A name designated by FDA through rulemaking, however, takes precedence over a USAN. 21 U.S.C. §§ 352(e), 358. The USAN and established name should not be confused with the international nonproprietary name (INN) assigned by the World Health Organization (WHO) to pharmaceutical substances and active ingredients, although with rare exceptions (e.g., acetaminophen / paracetamol) the names are identical.

164. See Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability, 80 Fed. Reg. 52,296-97 (Aug. 28, 2015). The agency also believes distinct names will also minimize “inadvertent substitution,” meaning “unintended alternating or switching of biological products that have not been determined by FDA to be interchangeable.”

165. FDA, NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY 1 (2015).

166. 80 Fed. Reg. at 52,296. Some have proposed relying on brand names or on the National Drug Code (NDC) number, which captures the manufacturer, strength, dosage form, formulation, and package (form or size) of a product. FDA appears to have rejected both. Although biosimilars are likely to have brand names, health care providers may use nonproprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of brand names. The NDC number is often omitted from adverse event reports or transcribed incorrectly. See generally Designation of Official Names and Proper Names for Certain Biological Products, 80 Fed. Reg. 52,224, 52,227 (Aug. 28, 2015); see also Erika Lietzan et al., *Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinguishable Nonproprietary Names for Biosimilars?*, 3 FDLI’S FOOD & DRUG POL’Y FORUM 6 (Mar. 27, 2013) (finding extensive use of reference product brand names to report adverse events experienced with generic products); *Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products Before FDA*, at 169 (Nov. 2, 2010) (statement of Dr. John K. Jenkins) (“[W]hile the [MedWatch] reporting system may include a field for NDC number, I think it’s very rare that we get that level of information . . .”).

Although controversial, FDA’s approach is similar to an approach offered privately by the generic industry, and it generally aligns with World Health Organization recommendations. Derrick Gingery, *GPhA Gets Its Second Choice on Biosimilar Naming*, PINK SHEET (Mar. 16, 2015), <https://pink.pharmamedtechbi.com/PS056721/GPhA-Gets-Its-Second-Choice-On-Biosimilar-Naming> [<https://perma.cc/87LF-PG4U>] (“[T]he trade group had actually

though the FTC staff argue that resulting confusion may slow uptake of biosimilars by deterring their usage, the case for confusion seems weak where two products share the same core name (e.g., “filgrastim”) and where the labeling of one states that it is a biosimilar of the other. It stands to reason that price considerations would prevail in this scenario, especially where payers play a role in treatment selection.

### C. *The Arrival of Interchangeable Biologics*

One of the most significant dynamic features of the biologic framework is the interchangeability determination. Although the biologic statute permits a biosimilar applicant to seek an interchangeability determination at the time of initial product approval, FDA has signaled that for now it expects applicants to proceed sequentially, beginning with biosimilarity.<sup>167</sup> At the time of writing, the agency had issued no interchangeability determinations.<sup>168</sup> But several important points stand out.

*First*, interchangeability determinations may be expensive for sponsors. In addition to meeting the standards for biosimilar licensure, the sponsor must show: (1) that its product can be expected to produce the same clinical result as the reference product in any given

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offered a close variant of the suffix naming idea to FDA during private meetings . . . .”); WHO, BIOLOGICAL QUALIFIER: AN INN PROPOSAL (2015), [http://www.who.int/medicines/services/inn/WHO\\_INN\\_BQ\\_proposal\\_2015.pdf](http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf) [<https://perma.cc/CV4J-MAPU>] (recommending assignment of random alphabetic codes—four random consonants with or without a two digit checksum—to the active substance applicant by applicant, to be used in conjunction with the product’s INN); see also Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J. L. & MED. 49 (2015) (examining the debate surrounding WHO international non-proprietary names for biologics and asserting that the outcome of the debate will affect cost-savings, effective tracking and reporting of adverse events, and barriers to market entry); Joanna M. Shepherd, *Biologic Drugs, Biosimilars, and Barriers to Entry*, 25 HEALTH MATRIX 139, 152 (2015) (arguing that pioneers have “sought to extend their current monopoly” by advocating for distinguishable non-proprietary names for biologics and by proposing bills in state legislatures “designed to impede the prescription of approved biosimilars in place of innovative biologics”).

167. FDA, GUIDANCE FOR INDUSTRY: BIOSIMILARS: ADDITIONAL QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009, at 7 (draft) (2015) [hereinafter FDA ADDITIONAL Q&A GUIDANCE], <http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf> [<https://perma.cc/MG59-Z97C>] (stating that “[a]t this time, it would be difficult as a scientific matter” for an applicant to establish interchangeability in an original application).

168. By way of contrast, FDA was issuing A-ratings *before* Congress enacted the Hatch-Waxman Amendments. The 1985 issue of the *Orange Book* was its sixth edition. FDA finally issued draft guidance on interchangeability in January 2017. FDA, GUIDANCE FOR INDUSTRY, CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (draft) (2017) [hereinafter FDA INTERCHANGEABILITY GUIDANCE], <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf> [<https://perma.cc/24WG-C9BM>].

patient, and, (2) if its product is administered more than once to an individual, the risk of alternating or switching between the products is not greater than the risk of using the innovative product alone.<sup>169</sup> FDA has said little since enactment about what will be needed to demonstrate the absence of an increased risk due to alternating or switching between the products. Prior to enactment, FDA indicated that it would want clinical switching studies to demonstrate the absence of an increased risk due to alternating or switching between the products,<sup>170</sup> and its recent draft guidance makes the same suggestion.<sup>171</sup> This could make interchangeability applications more expensive to prepare than biosimilarity applications. This stands in sharp contrast to the drug framework, where the easier and cheaper application—the ANDA—leads to the automatically substitutable product, and the harder and more expensive application—under section 505(b)(2)—generally leads to a product that is not substitutable and can be differentiated in the marketplace.<sup>172</sup> That said, as an institutional matter FDA is likely to prefer the eventual development of a paradigm where interchangeability determinations do not require extensive and expensive clinical studies.

*Second*, interchangeability determinations may not affect market penetration. In the case of physician-administered biologics, which comprise the vast majority, payers may drive patients to biosimilars through formulary coverage and design decisions regardless of any interchangeability determination. An interchangeability determination might have persuasive power if the biologic were indicated for patients suffering from chronic conditions and if the healthcare provider or payer were hesitant to switch patients stabilized on the reference product. But this incremental value could decline over time as payers and healthcare providers grow comfortable with non-medical switching and if immunogenic reactions are rare. In the case of self-

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169. 42 U.S.C. § 262(k)(4) (2012).

170. See *Biosimilars Implementation Hearing*, *supra* note 157; Letter from Frank M. Torti, M.D., M.P.H., Principal Deputy Comm'r and Chief Scientist, FDA, to Rep. Pallone, Chairman, H. Subcomm. on Health, Comm. on Energy and Commerce, at 9-10 (Sept. 2008) (stating that an interchangeability designation “would be based on, among other things, a showing of similar relevant structural characteristics between the two products, an understanding of the structure-function relationships, and clinical data evaluating the impact of switching patients from one product to the other”).

171. FDA INTERCHANGEABILITY GUIDANCE, *supra* note 168, at 9-16.

172. As a general rule, products approved pursuant to section 505(b)(2) could not be rated therapeutically equivalent. FDA grants therapeutic equivalence ratings if two drugs are pharmaceutically equivalent, which requires the same active ingredient, route of administration, dosage form, and strength, and if they are bioequivalent. See *supra* Section III.A. The very differences that lead to clinical testing and use of the 505(b)(2) pathway—such as tweaking the active ingredient—preclude a finding of pharmaceutical equivalence and therefore an A-rating.

administered biologics, payers may play a greater role in influencing market penetration through formulary design than would state pharmacy law through automatic substitution of interchangeable biologics. Whether the biologic is physician-administered or self-administered, if the healthcare provider or payer would select the biosimilar for the patient anyway, the interchangeability determination would not change the outcome and might not be worth the additional investment.

*Third*, although the statute offers exclusivity to the first applicant to demonstrate interchangeability, the market impact of this exclusivity is unclear, and the lead time may not justify the investment. The first biologic found interchangeable with a particular reference product for any condition of use receives a period of exclusivity during which no other biologic may be deemed interchangeable to that reference product for any condition of use.<sup>173</sup> In the meantime, however, FDA may apparently continue to approve biologics that are biosimilar to the same reference product. This is because the exclusivity provision prevents only interchangeability determinations; it does not prevent approval of biosimilars. So long as the agency expects interchangeability to be a sequential showing, there may be licensed biosimilars in the marketplace when the first sponsor demonstrates interchangeability, and additional biosimilars could launch during its exclusivity period. Moreover, even after the agency starts to license biosimilar biologics with immediate interchangeability determinations, the sponsors of those products could face competition from biosimilars during the exclusivity period. In either case, if interchangeability determinations add significant expense, if healthcare providers would select or payers would require use of the product even without the determination, and if payers would not absorb the cost of the determination, the period of time with exclusive interchangeability status may not justify the investment.<sup>174</sup>

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173. 42 U.S.C. § 262(k)(6) (2012). This exclusivity lasts for a maximum of one year, and the statute includes termination dates that operate as *de facto* forfeiture provisions if the sponsor does not launch in a timely fashion. *First*, if the innovator did not bring a patent infringement suit in accordance with section 351(l)(6), the exclusivity will end eighteen months after the interchangeable biologic was licensed. *Id.* § 262(k)(6)(C)(ii). *Second*, if the innovator brings a patent infringement suit, the exclusivity will end on the earlier of: (1) 18 months after a court decision or dismissal, or (2) 42 months after approval if the case is “still ongoing within” the 42-month period. *Id.* § 262(k)(6)(B)-(C).

174. See Derrick Gingery, *Biosimilar Interchangeability May Be Losing Luster as Approval Goal*, PINK SHEET (Sept. 13, 2016), <https://pink.pharmamedtechbi.com/PS119121/Biosimilar-Interchangeability-May-Be-Losing-Luster-As-Approval-Goal> [https://perma.cc/3EZE-HFHU] (quoting president and CEO of Momenta Pharmaceuticals, a biosimilar manufacturer, that “interchangeability cannot make up for late market entry,” that is, biosimilar biologics have already been approved for the reference product, an interchangeability designation “isn’t going to help you much at all”).

There is a great deal of uncertainty about interchangeability determinations, including how quickly they will become possible, whether they will be achievable for some products but not others, whether the associated cost will translate into more expensive products, and whether they will actually affect market penetration. On the one hand, interchangeable biologics could ultimately become the default, with biosimilar biologics a relic of the initial years of statutory implementation. On the other hand, interchangeability determinations could turn out to be mostly irrelevant and not worth the expense. The biosimilar industry does not have a uniform view on the value of interchangeability designations, perhaps due to differing research and development plans as well as different business models, which makes it difficult to predict what will happen.<sup>175</sup>

#### IV. INNOVATION: FUNCTIONAL AND CONCEPTUAL SEPARATION OF PATENTS

Enactment of a pathway for approval of abbreviated biologic applications fundamentally changed the hundred-year-old framework governing biological medicines.<sup>176</sup> It revolutionized how and on what terms biologic makers may compete in the marketplace, and it is equally likely to change when, how, and whether they innovate. As in the drug framework, the dimensions of competition and innovation should work synergistically; that is, a revolution in the competitive landscape will surely affect innovation decisions, and changes in innovation behaviors will surely affect the options for, if not the business strategies of, potential competitors. Evaluating the impact of this groundbreaking legislation on social welfare—whether, how, and why it results in pro-competitive versus anti-competitive behavior in the marketplace, and whether, how, and why it discourages versus stimulates innovation—requires careful attention to the ways in which it departs from the familiar generic drug framework.

Part 0 of this Article focused on the new pathway to market and the resulting marketplace and claimed that, unlike the generic drug pathway and marketplace, the biosimilar pathway and marketplace are highly variable and likely to evolve. This Part turns to the regulatory incentives for innovative behavior: data exclusivity and regulatory enforcement of patents.

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175. *See id.* (noting that Momenta no longer believes interchangeability important, but Sandoz views it as “an absolute key for our uptake of our biosimilars”).

176. Section 351 of the PHSA can be traced to the Biologics Control Act of 1902. Carver, Elikan, & Lietzan, *supra* note 35, at 682-83.

### A. Data Exclusivity as Research Motivator

Data exclusivity refers to the period of time after approval of an innovative application before any abbreviated application, seeking to rely on the innovator's research, may be submitted, or in some cases approved, by FDA.<sup>177</sup> There is an immediately noticeable difference between the two schemes: the exclusivity term for biologics is longer than the exclusivity term for drugs. A biosimilar application may not be submitted until four years after, and approval of that application may not be effective until twelve years after, first licensure of the reference product.<sup>178</sup> In contrast, a generic drug application may not be submitted until five years after approval of a new chemical entity (four years, if the generic company is challenging a patent held by the innovator), and in most cases where there is patent litigation, approval cannot be made effective until seven and a half years after approval of the new chemical entity.<sup>179</sup> Although the longer data exclusivity term for biologics has attracted a great deal of attention, the data exclusivity schemes differ in additional and more nuanced ways.<sup>180</sup>

*First*, the biologic framework does not provide separate exclusivity for post-approval innovation. Under the drug statute, if an innovator obtains approval of a new condition of use for its approved product—such as a new indication, route of administration, or dosage form—then an abbreviated application may not be approved for the same condition of use for three years.<sup>181</sup> By way of contrast, if a biologic innovator obtains approval of its product for a new indication, route of administration, dosage form, or other condition of use, it may be able

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177. Data exclusivity is different from market exclusivity. During a data exclusivity term, a subsequent applicant may not rely on the innovator's data; the abbreviated pathway to market is not available. Data exclusivity does not prevent subsequent applicants from obtaining approval on the basis of their own research. By way of contrast, market exclusivity prevents approval of *any* applications, including applications containing full data packages. The primary example is orphan drug exclusivity, for drugs that treat rare diseases. During the seven-year orphan drug exclusivity period, FDA may not approve the same drug for the same disease, even if proposed in a full application supported by original research. 21 U.S.C. § 360cc(a) (2012). See Lietzan, *supra* note 9, at 110-11 (explaining the difference between data and market exclusivity).

178. 42 U.S.C. § 262(k)(7) (2012). Professors Price and Rai have also argued that trade secrecy with respect to biologic manufacturing creates an additional barrier to entry that may “undermine” the “policy choice” that innovative biologics should have a “limited period of exclusivity.” See W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1062 (2016).

179. 21 U.S.C. § 355 (j)(5)(F)(ii)-(iv) (2012).

180. See generally Lietzan, *supra* note 9 (presenting a more detailed and functional discussion of these differences).

181. 21 U.S.C. § 355 (j)(5)(F)(iv). This exclusivity is available as long as the innovator submitted clinical data (other than bioavailability data) essential to approval of the new condition of use.

to patent the innovation in question, but the statute does not preclude approval of a biosimilar for that condition of use. Once the twelve years of exclusivity have expired, as a regulatory matter, subsequent innovations introduced by the innovator may be copied immediately.

*Second*, the biologic statute takes an all-or-nothing approach to structural innovations. If a drug innovator makes a structural modification to its previously approved active ingredient, and this results in a new active moiety, the new active moiety will be protected for five years. Any other structural modification will be protected for three years.<sup>182</sup> Put another way, either five years or three years will be available. In contrast, a biologic innovator's structural modification to its previously licensed biological product either results in twelve years of exclusivity or has no consequence whatsoever. That is, a modification to the structure of a biologic that results in a change in safety, purity, or potency results in a new "reference product," to which new four-year and twelve-year data exclusivity terms apply.<sup>183</sup> Anything short of that is treated like any other post-market innovation in the biologic framework; the innovator may be able to patent the innovation in question, but from a regulatory standpoint the innovation may be copied immediately.

*Third*, the statutes treat subsequent innovators differently, and this works synergistically with the differing approach to post-approval innovation. Twelve-year exclusivity is available for every biologic innovator that obtains approval of an active ingredient, rather than (as in the drug framework) only the first company to obtain its approval.<sup>184</sup> Thus, Teva received twelve years of exclusivity when FDA licensed Granix (tbo-filgrastim) in August 2012, despite the previous licensure of Amgen's Neupogen (filgrastim).<sup>185</sup> Had these products been subject to the drug statute, Teva would not have received the same five years of exclusivity that the innovator received; it would have received three years. The differential treatment of subsequent innovators is particularly important because the biologic statute: (1) does not give innovators any exclusivity for changes introduced to their own products, and (2) does not permit biosimilar applicants to propose modifications to reference products. In the drug

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182. *Id.* § 355 (j)(5)(F)(iii).

183. 42 U.S.C. § 262(k)(7)(A)-(C) (2012).

184. *See generally* Lietzan, *supra* note 9.

185. *See* FDA, LIST OF LICENSED BIOLOGICAL PRODUCTS WITH (1) REFERENCE PRODUCT EXCLUSIVITY AND (2) BIOSIMILARITY OR INTERCHANGEABILITY EVALUATIONS TO DATE (2017), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf> [<https://perma.cc/ZN9R-Q9ZL>].



framework, a subsequent applicant seeking to market a modified version of an innovative product—perhaps a modified active ingredient—may file a 505(b)(2) application, relying on the innovator's research, and still receive three years of exclusivity.<sup>186</sup> The innovator, if it makes those same changes, also receives three years of exclusivity. The two are on equal footing. In the biologic framework, a subsequent applicant seeking to market a modified version of an innovative product must file a full application, either performing the pre-clinical and clinical research itself (as Teva did) or paying for a right to reference the innovator's research.<sup>187</sup> But then it receives the full twelve years of exclusivity. By way of contrast, if the original innovator makes those same changes, it receives no exclusivity, even if it files a separate application. The two companies are not on equal footing.

Exclusivity in the biologic framework is product by product (application by application), rather than moiety by moiety.<sup>188</sup> Dispensing with the novelty inquiry in this way may make sense in the biologic setting; novelty inquiries have sometimes been challenging for FDA in the drug setting and may be even more challenging in the biologic setting.<sup>189</sup> The new approach is also consistent with understanding data exclusivity as an incentive for research and development behavior (specifically, the generation of data), conceptually distinct from patents, which protect property rights in inventions and thereby encourage inventive activity as well as disclosure and description of the resulting discoveries.

The biologic scheme's denial of exclusivity for an innovator's own post-market research may reflect this understanding of exclusivity as a research motivator. With respect to new information (such as a new medical use) and new product features (such as a new route of administration), the failure to provide exclusivity suggests a suspicion

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186. For instance, Sepracor earned three years of exclusivity in connection with its 505(b)(2) application for Xopenex® (levalbuterol hydrochloride), which is intended for treatment or prevention of bronchospasm in adults and adolescents with reversible obstructive airway disease. Levalbuterol is the R-enantiomer of albuterol, and the Xopenex application relied on Schering-Plough's approved NDA for Proventil® (albuterol). See Letter from Sepracor to FDA (May 23, 1997), [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/99/20837\\_Xenopex\\_admindocs.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20837_Xenopex_admindocs.pdf) [<https://perma.cc/K6U4-HKE8>] (identifying reference product); FDA, ORANGE BOOK ADA31 (20th ed. 2000) ADFNA31 (confirming three-year exclusivity). Even Omnitrope (somatropin recombinant), a follow-on version of Pfizer's Genotropin (somatropin recombinant), received three-year exclusivity. FDA, ORANGE BOOK 1013 (27th ed. 2007).

187. The competitor may obtain approval of its full application before the pioneer's data exclusivity expires. Data exclusivity blocks approval of biosimilar applications, not full applications. Patent considerations may prevent this second innovator from marketing its product, but the regulatory scheme will not. See generally Lietzan, *supra* note 9.

188. See Lietzan, *supra* note 9.

189. *Id.*

that the research in question is not socially productive when performed by the same company. Part 0 discusses this suspicion in more detail. With respect to structural modifications made by innovators, FDA has the opportunity to maintain the scheme's focus on research motivation, but much will turn on how the agency applies the exception to twelve-year exclusivity. Under the statute, a company's structural modifications to its own previously approved product do not receive exclusivity unless there is a resulting change in clinical profile. But the relationship between a biologic's structural attributes and clinical performance may not be fully understood, and the mechanisms of action may not be fully understood.<sup>190</sup> Even if eventually understood, they may not be understood until after a substantial amount of money has been invested. In order to preserve the scheme's focus on data exclusivity as a reward for research, FDA may need to presume a causal relationship if the structurally different molecule is demonstrated to be clinically different and causation is biologically plausible.

Regardless of how FDA interprets the provision relating to structural modifications, the biologic framework's product-by-product approach, providing the same twelve-year term for any company that undertakes the laborious and expensive process of compiling a full application, rather than inquiring into the novelty of the underlying active moiety, suggests a revised understanding of the role of data exclusivity. This seems significant in light of recent scholarship considering whether patent protection and exclusivity are functionally duplicative or, instead, achieve different goals, as well as legislative proposals that would allow innovators to choose between them.<sup>191</sup>

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190. See *supra* Part I.

191. See Yaniv Heled, *Why Primary Patents Covering Biologics Should be Unenforceable Against Generic Applicants Under the Biologics Price Competition and Innovation Act*, 21 ANNALS HEALTH L. 211, 221 (2012) (arguing that concurrent protection from primary patents and a 12-year exclusivity term "would cause waste and could lead to abuse of the patent system" but supporting "sequential" patent protection, for instance, for "secondary patents pertaining to substantial further developments of the originally approved biological product"); Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals-Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 423-24 (2012) (arguing that the exclusivity afforded to biologics is superior to patent protection and should replace primary patent protections once FDA has approved the pioneer); Christopher M. Holman, *Maintaining Incentives for Healthcare Innovation: A Response to the FTC's Report on Follow-On Biologics*, 11 MINN. J.L. SCI. & TECH. 755, 756 (2010) (arguing in favor of a twelve-year data exclusivity period and a "fair and nondiscriminatory" pre-approval patent dispute resolution process); Kristina M. Lybecker, *When Patents Aren't Enough: Why Biologics Necessitate Data Exclusivity Protection*, 40 WM. MITCHELL L. REV. 1427 (2014) (arguing that the Trans Pacific Partnership trade agreement should require participating countries to adopt twelve years of data exclusivity for biologics, in part because of earlier economic work showing the break-even period for biologics to range from thirteen to sixteen years); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 569-70 (2009) (arguing for an extension in exclusivity in

### B. *Quasi-Severance of Patents from the Regulatory Paradigm*

Just as data exclusivity is conceptually separated from the patent incentive in the biologic framework, the relationship between the regulatory scheme and the innovator's patent portfolio has been reworked. The biologic statute omits the regulatory reinforcement of patents that was the Hatch-Waxman legislation's greatest innovation and that has been propagated in U.S. international trade agreements. It also omits the regulatory incentives to achieving premarket resolution of patent disputes that have been the hallmark of the Hatch-Waxman scheme for more than thirty years.

#### 1. *Lack of Regulatory Reinforcement*

In the drug framework, the innovator's patents assume a direct regulatory role; the drug statute reinforces those patents. Each new drug applicant must identify the patents that claim its drug or a method of using its drug and with respect to which a claim of patent infringement could reasonably be asserted if another person manufactured, used, or sold the drug, without license to do so.<sup>192</sup> FDA lists the patents and their expiry dates in the *Orange Book*. Each generic applicant must address those patents in its application.<sup>193</sup> In the case of an unexpired patent, the generic applicant has two choices: to note the date that the patent will expire, or to assert that the patent is invalid or will not be infringed by the applicant's product. These are known as a "paragraph III" and "paragraph IV" certification, respectively, after the provisions of the statute in which they appear.<sup>194</sup>

The innovator's patents play a regulatory role, because the generic applicant's selection of paragraph III versus paragraph IV dictates when FDA may approve its application. If the generic applicant includes a paragraph III certification, then even if the generic drug approval standards are satisfied, final approval of the generic drug may

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order to capture unpatentable drugs); John A. Vernon et al., *Exploration of Potential Economics of Follow-On Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55, 56, 74 (2010) (arguing that the "considerable financial risk of biotechnology" research and development and its sensitivity to expected returns make it "critical" that Congress provide "a minimum of 17 years of data exclusivity or data protection" to ensure sufficient incentive for continued investment); see also Lietzan, *supra* note 9, at 122-30 (discussing functional differences between patent protection and data exclusivity for medicines, noting some of the key scholarship on this issue, and describing the MODERN Cures Act, which would allow companies to choose between exclusivity and patent protection).

192. 21 U.S.C. § 355(b)(1) (2012).

193. *Id.* § 355(j)(2)(A)(vii). With respect to a patent claiming a method of using the reference drug, a generic applicant may instead decline to seek approval of the use in question. *Id.* § 355(j)(2)(A)(viii).

194. *Id.* § 355(j)(2)(A)(vii) (III)-(IV).

not take effect until the patent expires.<sup>195</sup> If, instead, the generic applicant includes a paragraph IV certification, challenging the patent, then approval of the generic drug may take effect immediately, unless the NDA holder or patent owner brings suit within forty-five days.<sup>196</sup> If timely suit is brought, final approval of the generic application is stayed for thirty months.<sup>197</sup> At the end of the thirty months, FDA generally must approve the generic drug, even if the patent litigation is ongoing.<sup>198</sup> If a court finds the patent valid and infringed, it must order the effective date of final generic drug approval to be no sooner than patent expiry.<sup>199</sup> It may separately enjoin the generic applicant from commercial manufacture, sale, and use of the product.<sup>200</sup> Finally, the drug statute separately states that FDA approval may not take effect until the date specified by the court.<sup>201</sup>

The biologic statute provides none of this. There is no link between the timing of biosimilar licensure and the existence of, or disputes over, patents claiming the reference product. There is a scheme facilitating patent litigation prior to biosimilar market entry, but it is markedly different. The statute does not require biologic innovators to list their patents in their applications, nor does FDA publish a list of relevant patents. Instead, after the biosimilar application has been submitted, the two companies jointly and privately identify patents that may be at issue.<sup>202</sup> The biosimilar applicant must provide a detailed statement as to each patent either: (1) that it does not intend to market its product prior to patent expiry, or (2) why the patent is invalid, unenforceable, or not infringed.<sup>203</sup> These correspond conceptually to a paragraph III certification and a paragraph IV certification, respectively, in the drug statute, but they are provided to the innovator and not to FDA. Further, unlike the paragraph III certification, the corresponding statement in the biologic statute does not preclude FDA approval of the biosimilar application. It is simply a

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195. *Id.* § 355(j)(5)(B)(ii).

196. *Id.* § 355(j)(5)(B)(iii).

197. *Id.*

198. Specifically, assuming the approval standard has been met, FDA must approve the generic drug unless another generic applicant is eligible for 180-day exclusivity because it was the first to file a paragraph IV challenge to the innovator's patent(s). *See infra* note 208.

199. 35 U.S.C. § 271(e)(4)(A) (2012).

200. *Id.* § 271(e)(4)(B).

201. *See* 21 U.S.C. § 355(j)(5)(B)(iii)(II)(bb) (2012); *see also id.* § 314.107(b)(3)(B)(iii) (2016). In this case, FDA also requires the generic drug applicant to convert its paragraph IV certification to a paragraph III certification. *Id.* § 314.94(a)(12)(viii)(A). Once the paragraph III certification is in place, approval of the generic drug may not take effect until the patent expires. *Id.* § 355(j)(5)(B)(ii).

202. 42 U.S.C. § 262(l)(2)-(6) (2012).

203. *Id.* § 262(l)(3)(B)(ii)(I)-(II).

privately communicated statement of intent not to market prior to patent expiry. Nor is there a stay of FDA approval of the biosimilar in the event of timely suit on a patent claiming the reference product. Instead, after the companies select from the master list of patents a subset of patents for immediate litigation, the innovator faces penalties (discussed in the next subsection) if it fails to bring suit within thirty days.<sup>204</sup> There are no regulatory benefits to filing suit.<sup>205</sup> Moreover, unlike a prevailing drug patent owner, a prevailing biologic patent owner is not entitled to a court order setting the biosimilar approval date as the date of patent expiry. It is entitled to a statutory injunction of infringement, but only if it wins the case before data exclusivity expires.<sup>206</sup>

Thus, unlike the drug statute, the biologic statute does not reinforce the innovator's patents. If a biosimilar applicant declines to challenge a listed patent and chooses instead to delay market entry until the patent expires, it provides the innovator a statement to that effect—but FDA may license the biosimilar. If a biosimilar applicant asserts that a listed patent is invalid or not infringed, the innovator might institute patent infringement litigation—but FDA may license the biosimilar. If a court finds a listed patent valid and infringed, it might enjoin the biosimilar applicant from market entry—but the statute does not require the court to direct FDA not to license the biosimilar. The timing of licensure of a biosimilar will turn on regulatory considerations, such as the timing of the submission (itself informed by data exclusivity and presumably the applicant's assessment of the innovator's patent portfolio) and the quality of the submission.

## 2. Omission of Regulatory Incentives to Resolve Patent Issues

The biologic statute also omits any regulatory incentives to resolve patent issues prior to biosimilar approval and launch. This stands in stark contrast to the drug statute, which includes provisions de-

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204. If the parties do not reach an agreement, the statute creates a procedure for determining which patents will be litigated immediately. *Id.* § 262(l)(5).

205. The statutes specify one role for FDA in the patent litigation scheme. Within thirty days of service of a complaint for patent infringement, the biosimilar applicant must provide FDA with notice and a copy of the complaint. FDA, in turn, must publish notice of that complaint in the Federal Register. *Id.* § 262(l)(6)(C). The statute imposes no deadline for publication of this notice, and they have been running several months behind. *E.g.*, Receipt of Notice That a Patent Infringement Complaint Was Filed Against a Biosimilar Applicant, 81 Fed. Reg. 18,858 (Apr. 1, 2016) (notice of October 2, 2015, complaint).

206. Compare 35 U.S.C. § 271(e)(4)(A) (2012) (requiring court to order that generic drug approval be postponed to patent expiry), with *id.* § 271 (e)(4)(D) (requiring injunction of infringement by biosimilar applicant provided the biosimilar applicant has not yet been approved, due to data exclusivity).

signed to incentivize both innovators and generic applicants to participate in premarket patent litigation. The drug statute encourages patent challenges by permitting a generic applicant that challenges a patent claiming a new chemical entity, or a method of using the new chemical entity, to submit its application four years—rather than five years—after FDA approval of the innovative product in question.<sup>207</sup> It further encourages patent challenges by providing that, regardless of whether the innovative product was a new chemical entity, the first generic applicant to include a patent challenge in its ANDA is eligible for 180 days of exclusivity against subsequent generic challengers.<sup>208</sup> Finally, the drug statute encourages innovators to bring patent litigation promptly, by offering a thirty-month stay of generic approval if suit is brought within forty-five days of notice of a patent challenge.<sup>209</sup>

The biologic framework takes a fundamentally different approach. Where the drug scheme dangles carrots, the biologic scheme threatens with a stick. To begin with, a biosimilar applicant that challenges an innovator's patent will receive no regulatory benefits. It may not submit its application any earlier, nor does the first to challenge the patent become eligible for exclusivity. Also, an innovator that initiates premarket litigation within the thirty-day window receives no regulatory benefits; there is no stay of biosimilar approval. Instead, the innovator and patent owner face penalties for their failure to follow the premarket patent litigation process laid out in the statute. Specifically, if the innovator does not initiate patent litigation within the window, or does but the suit is dismissed without prejudice or not prosecuted in good faith, it may recover only a reasonable royalty for infringement of the patent.<sup>210</sup> Moreover, if the patent should have been, but was not, included on the innovator's initial list of patents, the patent owner may not bring suit on that patent under section 271 of the Patent Act with respect to that biosimilar product.<sup>211</sup>

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207. 21 U.S.C. § 355(j)(5)(F)(ii) (2012).

208. *Id.* § 355(j)(5)(B)(iv). See generally Erika Lietzan & Julia Post, *The Law of 180-Day Exclusivity*, 71 FOOD & DRUG L.J. 327 (2016).

209. 21 U.S.C. § 355(j)(2)(B)(ii), (iii), (iv) (2012). If the reference product is a new chemical entity and the litigation begins during the fifth year after its approval, the stay is lengthened to toll generic approval until seven and a half years after new chemical entity approval. *Id.* § 355(j)(5)(F)(ii).

210. 35 U.S.C. § 271(e)(6)(A), (B) (2012).

211. *Id.* § 271(e)(6)(C). If a patent issues to, or is exclusively licensed by, the innovator after the initial list has been generated, the innovator has thirty days to supplement its list. 42 U.S.C. § 262(l)(7) (2012). The same penalty provision then applies. If the patent should have been listed and was not, the patent owner may not bring suit on that patent with respect to that biosimilar product. 35 U.S.C. § 271(e)(6)(C) (2012). It has been suggested that the penalty provision simply precludes patent infringement litigation under subsection 271(e)(2) rather than all of section 271 of the Patent Act. Brian D. Coggio, *Can*

The consequences for a biosimilar applicant that fails to follow the process are much less significant. The statute describes consequences that stop short of penalty. If the biosimilar applicant fails to provide a copy of its application to the innovator, the innovator may bring a declaratory judgment action on certain patents, assuming it is aware of the biosimilar application, but the biosimilar applicant may not bring a declaratory judgment action.<sup>212</sup> The biosimilar applicant faces a similar consequence if it provides its application but fails to take any of the subsequent steps in the process, such as asserting a position on each listed patent. That is, the innovator may bring a declaratory judgment action, but the biosimilar applicant may not.<sup>213</sup> The innovator cannot obtain a federal injunction ordering the biosimilar application to provide its application, and presumably it cannot obtain an injunction ordering the biosimilar application to comply with any of the subsequent steps.<sup>214</sup> In the end, meaningful adverse consequences for the biosimilar applicant will derive from a court finding of infringement, not from its refusal to participate in the premarket patent process.

## V. IMPLICATIONS AND CONCLUSION

The goals of the 2010 biosimilar biologic statute were essentially the same as the goals of the 1984 generic drug statute: to enable cost-

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*Reference Sponsor Forfeit Right to Sue Under BPCIA?*, LAW 360 (July 25, 2016, 12:51 PM), <https://www.law360.com/articles/820197/can-reference-sponsor-forfeit-right-to-sue-under-bpcia>. This would preclude premarket patent litigation, for which federal court jurisdiction is made possible by an artificial act of infringement tied to the patent challenge. The argument requires a strained reading of the term “section” in the penalty provision, but if correct would mean that the innovator and patent owner could still bring suit once the biosimilar applicant launched.

212. 42 U.S.C. § 262(l)(9)(C) (2012). The PHSA authorizes an action for declaratory judgment under 28 U.S.C. § 2201 in this case, but only with respect to a patent claiming the reference product or a method of using the reference product. The Patent Act deems submission of the biosimilar application an artificial act of infringement with respect to a broader group of patents—any patent that could have been identified if the biosimilar applicant had provided its application. 35 U.S.C. § 271(e)(2)(C)(ii) (2012).

213. *Id.* § 262(l)(9)(B). In this case the PHSA authorizes a declaratory judgment with respect to any patent identified by the reference product sponsor in the first step of the information exchange process.

214. *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1675 (2017) (holding that reference product sponsors do not have access to injunctive relief, at least as a matter of federal law, to enforce the disclosure requirement). Although the reference product sponsor cannot enforce the requirement to provide a copy of the biosimilar application in federal court, it remains to be seen whether remedies might be available under state law. *Id.* It is also at least theoretically possible that the federal government will decide to enforce the requirement. *E.g.*, *id.* n.2 (referring to a “violation” of the requirement in § 262(l)(2)(A) to provide a copy of the application); 42 U.S.C. § 262(f) (deeming it a misdemeanor to “violate” any provision of section 262); *see also Sandoz*, 137 S. Ct. at 1678 (Breyer, J., concurring) (noting that Congress had implicitly delegated authority to interpret these provisions to FDA).

savings for the healthcare finance system by facilitating approval of lower priced versions of higher priced innovative medicines, while stimulating innovation, or at least preserving incentives to innovate. Both statutes require a delicate balance of static and dynamic welfare considerations: the desire for less expensive versions of already available innovative products, on the one hand, and the desire for improved innovative products and new cures, including cures for untreated or poorly treated conditions, on the other hand. The approach taken in 2010 for biological medicines is, however, profoundly different from the approach taken in 1984 for conventional drugs.

Part 0 of this Article describes a framework for approval, promotion, pricing, reimbursement, and uptake of biosimilar biologics that is complex, variable, evolving, and unlike anything that scholars and courts have seen previously. Part 0 describes a refined view of data exclusivity as an incentive for research rather than invention, as well as a disentanglement of patents from the regulatory approval statute. Together Parts 0 and 0 suggest that with respect to both competition and innovation, we are now in uncharted waters. The new paradigm invites important theoretical and empirical work on innovation and competition in biologic medicines in the years ahead. This Part concludes with some speculation about how these differences may work synergistically and why they may matter.

To begin with, there may be cause for concern that the new biologic framework provides insufficient incentive for post-approval innovation by biologic innovators, meaning the development of new information and the development of new products. An innovator receives no supplemental exclusivity for new indications or other new labeling information, even if supported by extensive and expensive research. The information in question—whether developed after five years, ten years, or fifteen years—will be protected only until twelve years after the product was first licensed. This may be concerning because recent developments in patent law could undermine the incentive to discover new information.<sup>215</sup> The value of patent protection may be modest here in any case, because the patent is not enforced by the biologic regulatory scheme, and because healthcare providers and patients use approved products in ways that deviate from the approved labeling and that infringe patents.

There may also be insufficient incentive for innovators to develop new product features, such as new formulations, routes of admin-

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215. *E.g.*, *Mayo Collaborative Servs. v. Prometheus Labs.*, 566 U.S. 66 (2012) (invalidating a claim for a method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder with thiopurine, which relied on the previously unknown correlations between metabolite levels and likely harm or ineffectiveness).



istration, and dosage forms. Like new information, new product features receive no supplemental exclusivity. As a regulatory matter, they will be protected only until the originally approved product is vulnerable to biosimilars—twelve years after first licensure. The innovator's ability to recoup its investment in new product features will depend on the features having both clinical significance and strong patent protection. Clinical significance may not be evident until after significant investments have been made, which may mean that investments will simply not be made. And strong patent protection may not align with clinical benefit in the case of a medicine, as the inquiries are different.<sup>216</sup>

The net result could be loss of important innovation with respect to already marketed biologics. Although it may be difficult to quantify or characterize the research that is forewarned in the new biologic framework, the dramatically different approach to post-market research and product innovation surely calls for close attention to the possibility of a decline.

As a historical matter, the biologic statute's uncharitable approach to post-market innovation by pioneers may stem from concerns about supposedly anti-competitive innovation in the drug marketplace, called "product hopping" by its detractors. A closer look, however, illustrates the problem with simply borrowing assumptions from the generic drug literature. The essence of the argument in the drug setting is that it is exclusionary for an innovator to introduce a patented (or exclusivity-protected) second generation version of its product shortly before the patents or exclusivity on the first generation version expire, particularly if the end result is that physicians and patients switch to its newer product rather than using the generic version of its first generation product.<sup>217</sup> Sometimes the innovator's advertising and promotion persuades physicians and patients to adopt the newer product, and detractors voice suspicion that these individuals switched to the more expensive product even when switching was not medically indicated. In other cases, it is argued, market withdrawal of the first-generation product forces patients to

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216. See Lietzan, *supra* note 9, at 125-26.

217. See, e.g., Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685, 687 (2009) (referring to "product hopping"—where "the branded company makes repeated changes in a drug's formulation to prevent generic substitution, rather than to improve the efficacy of the drug product"—as an "exclusionary tactic"); Aaron S. Kesselheim & 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 293, 336-40 (2015) (describing "strategic introduction of a slightly modified form of the product just prior to patent expiration," suggesting that "timing" is an important clue as to the company's purpose, and suggesting that statutory changes might be appropriate if "a clear pattern of abuse" goes uncorrected in the courts).

switch to the newer product, and inertia prevents them from switching back once a generic is approved. Ultimately, the concern is that generic copies of the first-generation product will not achieve market penetration, because the business model of generic companies involves reliance on automatic substitution, and physicians will no longer write prescriptions for the innovator's first-generation product. The lack of generic market penetration, the argument goes, deprives the healthcare finance system of the substantial cost-savings that were expected when the innovator's first product reached patent and exclusivity expiry. Lawsuits challenging these post-market innovation and marketing decisions on antitrust grounds have been winding their way through the federal courts for more than a decade, with mixed results.<sup>218</sup>

A different and more complex analysis may be necessary in the biologic framework, at least in the short term and at least with respect to biosimilar biologics. Biosimilar applicants will likely obtain market share by persuading formulary committees, healthcare providers, and pharmacy benefit managers to select their products over the corresponding reference products. Their ability to do so may depend on the cost savings they are able to offer, which in turn may depend on the premarket burden they face, and this could depend in turn on FDA's interpretation and implementation of the new pathway (which could evolve) as well as issues specific to the product class or product at issue. Their ability to persuade these deci-

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218. *Compare* New York v. Actavis PLC, 787 F.3d 638 (2d Cir. 2015) (ruling that an innovator could not stop selling its immediate release formulation of a particular drug—in favor of a newer, patented, extended release formulation—until thirty days after approval of the first generic versions of the immediate release product), *with* Mylan Pharms. v. Warner Chilcott, 838 F.3d 421 (3d Cir. 2016) (affirming summary judgment in case involving three reformulations of Doryx® (doxycycline hyclate) combined with ceasing sales of, and buying back, prior formulations, and promotion of the new formulations). The district court in Pennsylvania concluded that a generic company may reach consumers through advertising, promotion, cost competition, or superior product development, and that if it chooses instead to rely on automatic state substitution laws, it is a “victim” of its own business strategy. Mylan Pharms. v. Warner Chilcott, Civ. No. 12-3824, 2015 WL 1736957 (E.D. Pa. 2015). The Court of Appeals quoted, approvingly, the district court's comment that Warner Chilcott had “no duty to facilitate Mylan's business plan by keeping older versions of branded Doryx on the market.” *Mylan Pharms.*, 838 F.3d at 432. Outcomes at the district court level have varied somewhat with the facts. *See In re* Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig., 64 F. Supp. 3d 665 (E.D. Pa. 2014) (denying motion to dismiss in case involving introduction of Suboxone® film and potential removal of Suboxone® tablets due to safety concerns); *Walgreen Co. v. AstraZeneca Pharms. L.P.*, 534 F. Supp. 2d 146 (D.D.C. 2008) (granting motion to dismiss Sherman Act complaint relating to introduction, and promotion, of Nexium® (esomeprazole) eight months before expiry of patents on Prilosec® (omeprazole)); *Abbott Labs. v. Teva Pharms. USA*, 432 F. Supp. 2d 408 (D. Del. 2006) (denying motion to dismiss in case involving two formulation changes to Tricor® (fenofibrate), one from capsules to tablets and the other from one tablet to another, and efforts to remove capsules from the marketplace).

sionmakers could also turn, for now, on other factors, such as the immunogenicity profile of the molecule and the number of newly diagnosed (treatment-naïve) patients each year, or brand loyalty on the part of healthcare providers (which may vary). Further, because biosimilar applicants seem inclined to provide only modest discounts in the immediate term, and because biosimilar market share will depend on competition rather than automatic substitution, many expect innovators to continue marketing their first-generation products after biosimilar market entry. This suggests that the development, patenting, and introduction of a second-generation innovative product may simply give decisionmakers a *third* product in the class from which to select. Whether or not the innovator continues to market its original product, the presence of a second-generation innovative product in the marketplace will not preclude biosimilar applicants from employing the primary mechanism by which they obtain market share: promotion, presumably mostly on the basis of cost-savings, to payers. Further, it is not unreasonable to hypothesize that rational payers will push physicians and patients to biosimilars of the first-generation product unless the second-generation product is not only clinically superior but also comparatively cost-effective.

Closely connected to incentives for post-approval innovation and the question of product hopping are the incentives for subsequent applicants themselves, specifically the pathway choices they face. Here it may be highly relevant that in the biologic framework, the classic industry bifurcation—innovators on the one hand and generic companies on the other hand—has evaporated. To give a concrete example, Amgen holds the approved application for the first reference product to be cited (Neupogen) as well as the approved application for the fourth biosimilar to be approved (Amjevita, a biosimilar of Humira). The significant investment needed to develop, manufacture, and market a biosimilar has so far limited the field to larger firms, mainly innovators with biologic expertise. Any such applicant considering its own version of a previously approved biological product necessarily faces a choice whether to use the biosimilar pathway or instead file a full application. The choice is complex.<sup>219</sup> On the one hand, the biosimilar pathway is less expensive than the full pathway, and a biosimilar applicant may use the highly advantageous process of extrapolation to justify a broad approval for patient populations and indications that it has not clinically tested.<sup>220</sup> Further, an interchangeability determination is a possibility. On the other hand, with the biosimilar pathway there is no scope to make improvements or

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219. Lietzan, *supra* note 9, at 162.

220. See HEALTH CANADA, *supra* note 71.

modifications to the molecule, or to propose new uses, nor is it possible to deviate with respect to route of administration, dosage form, or strength in order to avoid a patent. The strict-duplication rule could stimulate price competition among a reference product and its biosimilars, but the innovative firms are not accustomed to competing in this manner without any basis for product differentiation.

The differences in the biosimilar framework suggest that the “product hopping” cases and literature from the drug framework may not be relevant. If true, then reliance on this history to justify a cramped approach to post-approval innovation in the biologic statute was misplaced. Arguably this makes it even more imperative to watch closely for the possibility that the scheme’s failure to reward post-market innovation causes harm in the form of innovation not undertaken. The “product hopping” discussion also suggests that what is viewed as anticompetitive in one framework may not have the same practical impact, in the other. Consequently, scholars and courts would do well to consider the myriad differences in the biologic framework before assuming the relevance of analysis and empirical scholarship from the drug scholarship. This is not to say that choices criticized in the drug framework will not emerge, or merit concern, in the biologic framework. The claim is only that these waters are different and deeper, and robust scholarship should take stock of those differences. Moreover, the variability and dynamism of the biologic framework mean that scholars and courts will need to engage in iterative assessments. What is true of one biologic may not be true of another biologic. What is true in one year might not be true three years later.

Over time, the evolution in the framework may create an opportunity for new scholarship comparing the different approaches to innovation. The dynamism could mean that eventually significant portions of the biologic framework come to resemble the corresponding aspects of the drug framework. Without any change in the legislation, in another decade or two, FDA could be approving mostly interchangeable biologics (rather than biosimilar biologics) and mostly on the basis of (generic-like) analytical and pharmacokinetic applications. Working in conjunction with state pharmacy law, distribution models and reimbursement policies could evolve to ensure automatic use of interchangeable biologics in this scenario. In this hypothetical evolved world, the primary remaining difference between the drug framework and biologic frameworks might be the profound difference in innovation policies discussed in Part 0. This could set up a natural experiment, allowing comparison of the two approaches and possibly leading us to better data-driven conclusions about the approach that best furthers social welfare.

