

# BIOSIMILAR BIAS: A BARRIER TO ADDRESSING AMERICAN DRUG COSTS

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## ABSTRACT

Forty percent of spiraling drug costs in the United States stem from a mere 2% of all drugs—biologic drugs (biologics) made from living cells and administered by injection or infusion. Drug costs will continue to rise as new biologics are approved by the Food and Drug Administration. Biologics are expensive because they cannot be mass-produced, and the consequence of their high prices is that important treatments for conditions such as arthritis and cancer remain out of reach for many Americans. Fortunately, just as there are lower cost generic versions of brand-name pills, there are lower cost biosimilars of original biologics—the lower cost is made possible by an expedited regulatory approval process. Despite the lower cost and a decade of safe biosimilar use globally, U.S. adoption of biosimilars remains minimal, in stark contrast to widespread use of generic drugs.

This Article provides the first comprehensive explanation of how U.S. laws, industry actions, and cognitive biases work together to impede the use of biosimilars in the United States. This Article argues that doctors and patients currently have unfounded misperceptions concerning the safety and efficacy of biosimilars based on misinformation propagated by companies that builds upon an existing cognitive bias against cheaper drugs. These misperceptions keep drug costs high and lead to worse health outcomes for patients—studies have shown that these unfounded misperceptions can have negative physical manifestations. Although there is a similar misperception against generic drugs, generic drugs do not face the structural barriers in regulatory laws and insurance coverage that exacerbate biases against biosimilars. For example, U.S. regulatory law requires an additional regulatory designation to permit a pharmacist to substitute a biosimilar without doctor intervention. No such additional regulatory designation is required for substituting generics.

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After revealing the existence and extent of the bias against biosimilars, this Article proposes solutions to effectively promote and increase biosimilar use. It suggests a multipronged approach to encourage biosimilar use, including legal changes to support biosimilar substitution, education to specifically tackle biases, and financial incentives to encourage biosimilar use. Addressing barriers to biosimilar use would not only expand access to treatment but would also save the United States an estimated \$50 billion in the next decade.

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## INTRODUCTION

There is a major problem with containing costs for the most expensive drugs in the U.S. market. In particular, complex drugs made from living biological compounds (biologics) constitute about 40% of drug costs,<sup>1</sup> despite being only 2% of drugs used.<sup>2</sup> Biologics include revolutionary treatments such as the mRNA-based COVID-19 vaccines by Pfizer and Moderna,<sup>3</sup> Humira for arthritis,<sup>4</sup> and Herceptin for some types of breast cancer.<sup>5</sup> However, biologic costs can be substantial, with retail prices that are easily \$10,000–\$70,000 per year per patient and some costing

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1. IQVIA, BIOSIMILARS IN THE UNITED STATES 2020–2024: COMPETITION, SAVINGS, AND SUSTAINABILITY 3 (2020); *see also* ASSISTANT SEC’Y FOR PLAN. & EVAL., MEDICARE PART B DRUGS: TRENDS IN SPENDING AND UTILIZATION, 2006–2017 9 (2020) [hereinafter ASPE SPENDING TRENDS] (finding biologics administered in medical offices constitute almost 80% of Medicare Part B drug costs).

2. *E.g.*, Avik Roy, *Biologic Medicines: The Biggest Driver of Rising Drug Prices*, FORBES (Mar. 8, 2019, 8:20 PM), <https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices>.

3. *E.g.*, *Pfizer and BioNTech Initiate Rolling Biologics License Application for U.S. FDA Approval of Their COVID 19 Vaccine*, PFIZER (May 7, 2021, 6:45 AM), <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-rolling-submission-biologics>; *Moderna Initiates Rolling Submission of Biologics License Application for its COVID-19 Vaccine*, BIOPHARM INT’L (June 2, 2021), <https://www.biopharminternational.com/view/moderna-initiates-rolling-submission-of-biologics-license-application-for-its-covid-19-vaccine>.

4. *E.g.*, Benita Lee, *What are Biologics? 5 Examples of Drugs You May Already Be Taking*, GOODRX (June 13, 2018), <https://www.goodrx.com/blog/biologics-biological-drugs-examples> (discussing biologics such as Humira and Botox); Kathlyn Stone, *Top 10 Biologic Drugs in the United States*, VERYWELL HEALTH (Oct. 11, 2021), <https://www.verywellhealth.com/top-biologic-drugs-2663233>.

5. *See* George W. Sledge, Eleftherios P. Mamounas, Gabriel N. Hortobagyi, Harold J. Burstein, Pamela J. Goodwin, & Antonio C. Wolff, *Past, Present and Future Challenges in Breast Cancer Treatment*, 32 J. CLINICAL ONCOLOGY 1979, 1979, 1983 (2014). In addition, biologics have recently been developed as a preventative treatment to reduce debilitating migraines by up to 50%. *E.g.*, Philip Harvey, Pooja Shah, & Scott Shipley, *An Overview of New Biologics for Migraine Prophylaxis*, 45 U.S. PHARMACIST 21, 21 (2020).

hundreds of thousands per year or more.<sup>6</sup> Even after insurance, biologics can cost patients \$8,000–\$40,000 per year.<sup>7</sup> High costs are a barrier to effective treatment because patients forgo or ration treatment, leading to poor health outcomes,<sup>8</sup> including unnecessary deaths for diabetic patients who skip insulin doses.<sup>9</sup> Moreover, expensive biologics may exacerbate known income disparities in accessing drugs because those with fewer resources are often unable to afford recommended treatment.<sup>10</sup> This is especially true if doctors prescribe originator biologics—the first-to-market biologic medicine, analogous to the first-to-market brand drug that precedes a generic—instead of lower-cost biosimilars, which are highly similar, subsequent to the originators, and intended to lower prices, similar to generic versions of traditional drugs.

Although competition generally results in lower prices, effective competition is currently stymied for U.S. biologics. A streamlined regulatory approval process for traditional drugs results in many low-cost generic drugs, which account for 90% of prescriptions.<sup>11</sup> However, a decade after the United States finally adopted a similar process for subsequent biologics, biosimilars constitute less than 30% of the U.S. biologics

6. See Favour Danladi Makurvet, *Biologics vs. Small Molecules: Drug Costs and Patient Access*, 9 MED. DRUG DISCOVERY 100075, at 4 (2021) (noting that the daily cost of biologics is twenty-two times that of other drugs); Mike Z. Zhai, Ameet Sarpatwari, & Aaron S. Kesselheim, *Why are Biosimilars Not Living Up to Their Promise in the US?*, 21 A.M.A. J. ETHICS 668, 668 (2019) (noting costs in excess of \$100,000 per year); Victor L. Van de Wiele, Aaron S. Kesselheim, & Ameet Sarpatwari, *Barriers to US Biosimilar Market Growth: Lessons from Biosimilar Patent Litigation*, 40 HEALTH AFFS. 1198, 1198 (2021) (observing that many biologics cost more than \$100,000, including some newer ones costing severalfold higher). Biologics are the most expensive drugs covered by Medicare, representing 43% of drug spending for physician-administered drugs. ALEX BRILL, SHARED SAVINGS DEMONSTRATION FOR BIOSIMILARS IN MEDICARE: AN OPPORTUNITY TO PROMOTE BIOLOGIC DRUG COMPETITION 5 (2020).

7. See ASPE SPENDING TRENDS, *supra* note 1, at 11; see also WAYNE WINEGARDEN, PROMOTING BIOSIMILAR COMPETITION TO REDUCE PATIENTS' OUT-OF-POCKET COSTS 7–11 (2020) (comparing annual costs of originator biologics (\$4,000 to over \$60,000) to biosimilars (\$30,000 to over \$40,000)); Sonal Parasrampur & Gerald F. Anderson, *Comparing Patient OOP Spending for Specialty Drugs in Medicare Part D and Employer-Sponsored Insurance*, 26 AM. J. MANAGED CARE 388, 391 (2020) (noting out-of-pocket costs for originator biologics range from around \$200 to nearly \$2,000 a month); Sarah Jane Tribble, *Why the U.S. Remains the World's Most Expensive Market for 'Biologic' Drugs*, KAISER HEALTH NEWS (Dec. 20, 2018), <https://khn.org/news/u-s-market-for-biologic-drugs-is-most-expensive-in-the-world>.

8. Patient compliance with drug treatment is negatively correlated to cost. *E.g.*, Jack Burks, Thomas S. Marshall, & Xiaolan Ye, *Adherence to Disease-Modifying Therapies and Its Impact on Relapse, Health Resource Utilization, and Costs Among Patients with Multiple Sclerosis*, 9 CLINICOECONOMICS & OUTCOMES RES. 251, 259 (2017); Parvaneh Heidari, Wendy Cross, & Kimberley Crawford, *Do Out of Pocket Costs Affect Medication Adherence in Adults with Rheumatoid Arthritis? A Systematic Review*, 48 SEMINARS ARTHRITIS & RHEUMATISM 12, 18–20 (2018).

9. See Bram Sable-Smith, *Insulin's High Cost Leads to Lethal Rationing*, NPR (Sept. 1, 2018, 8:35 AM), <https://www.npr.org/sections/health-shots/2018/09/01/641615877/insulins-high-cost-leads-to-lethal-rationing>.

10. High drug costs are known to exacerbate racial and income disparities in medication use. See Stephen J. Kogut, *Racial Disparities in Medication Use: Imperatives for Managed Care Pharmacy*, 26 J. MANAGED CARE SPECIALTY PHARMACY 1468, 1468 (2020).

11. 21 U.S.C. § 355(j) (permitting abbreviated applications for approval of generic drugs); ASS'N FOR ACCESSIBLE MEDS., SECURING OUR ACCESS & SAVINGS: 2020 GENERIC DRUG & BIOSIMILARS ACCESS & SAVINGS IN THE US REPORT 16 (2020) [hereinafter AAM 2020 ACCESS & SAVINGS] (noting generics are 90% of prescriptions filled).

market.<sup>12</sup> Of the seven originator biologics that have a biosimilar in the United States, only one has biosimilars that capture more than 50% of the market share.<sup>13</sup>

This Article provides the first comprehensive explanation of how pervasive individual cognitive biases, in conjunction with pharmaceutical mismarketing and structural components in U.S. law and insurance policies, have perpetuated illogical biases against biosimilars. Marketing may cause a doctor to refuse to prescribe biosimilars based on a false belief that biosimilars are not as effective as the originator biologic even though the Food and Drug Administration (FDA) has determined the biosimilar to be highly similar to the originator, safe, and effective.<sup>14</sup> Understanding that cognitive biases may perpetuate bias against biosimilars is essential because it means that simply ending mismarketing and even dismantling some structural components may not be fully effective in dispelling the bias. Studies indicate that cessation of erroneous statements may inadequately correct years of false advertising and even retractions may be ineffective to reduce misinformation.<sup>15</sup> Accordingly, proposed action—such as the FDA and Federal Trade Commission (FTC) announcement that they will aim to stop misinformation concerning biosimilars—is alone likely inadequate to reduce misperceptions and promote desired biosimilar usage.<sup>16</sup> A better understanding of the existence and extent of the bias against biosimilars, as well as cognitive biases and structural issues that perpetuate these biases, is essential to develop effective and realistic solutions to promote the cost-saving use of biosimilars in the United States.<sup>17</sup>

There are significant structural issues, in addition to influential advertising, that promote and exacerbate bias against biosimilars in a much more problematic manner than with generics. As this Article explains, although there is a similar bias concerning generics, financial incentives and federal and state laws incentivize generic use, but *disincentivize* biosimilar use. For example, lower cost generics are promoted largely by state laws

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12. ASS'N FOR ACCESSIBLE MEDS., THE U.S. GENERIC & BIOSIMILAR SAVINGS REPORT 21 (2021) (data as of 2020).

13. NORC, UNDERSTANDING STAKEHOLDER PERCEPTION OF BIOSIMILARS 1 (2021); Katie Holcomb, Michelle Klein, & Michelle Wang, *Biosimilars in the Medicare Part B Market*, MILLIMAN WHITE PAPER 3 (2021) (noting that Zaxxio is over 50% but all other biosimilars are less than 20% and many less than 10%).

14. See generally discussion *infra* Parts II & III.

15. E.g., Stephan Lewandowsky, Ullrich K. H. Ecker, Colleen M. Seifert, Norbert Schwarz, & John Cook, *Misinformation and Its Correction: Continued Influence and Successful Debiasing*, 13 PSYCH. SCI. PUB. INT. 106, 114 (2012).

16. See FDA & FTC, JOINT STATEMENT OF THE FOOD & DRUG ADMINISTRATION AND THE FEDERAL TRADE COMMISSION REGARDING A COLLABORATION TO ADVANCE COMPETITION IN THE BIOLOGIC MARKETPLACE (Feb. 3, 2020).

17. Addressing biosimilar use is a complex problem that includes scientific and legal uncertainties as well as anticompetitive conduct by companies that block entry of biosimilars approved by the FDA. E.g., Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1, 3 (2018). See generally W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1037–56 (2016). The current discussion complements other proposals because doctor and patient acceptance of biosimilars is essential to their success.

that encourage or mandate pharmacy substitution of the generic (unless the prescription indicates otherwise); this cannot happen with most biosimilars because they are not sold in pharmacies.<sup>18</sup> Rather, because most biologics are administered by health-care providers in their offices, there is no opportunity for a pharmacy to promote substitution of a cheaper biosimilar. In addition, for the minority of biologics sold in pharmacies, substitution is challenging because it is only permissible for biosimilars that meet the regulatory designation of “interchangeable,” a designation not required of generics.<sup>19</sup> However, even biosimilars with the interchangeable designation may still not be substituted due to state laws that impose additional hurdles, unlike the situation with generics.<sup>20</sup> Moreover, payor incentives (i.e., insurance coverage) often do not favor biosimilars in contrast to incentives for generics.<sup>21</sup> Additionally, although doctors and patients are generally accustomed to generics having the identical active ingredient as their brand counterparts, biosimilars are scientifically incapable of being identical and are far more complex than a single active ingredient.<sup>22</sup> Originator biologic manufacturers have capitalized on the fact that biosimilars are not identical in their marketing materials and have also suggested falsely that only biosimilars with the unique U.S. regulatory designation of interchangeable are safe, further fueling unnecessary bias.<sup>23</sup>

A better understanding of bias against cost-effective biosimilars is helpful not only to address unnecessary health costs, but also to lead to better patient outcomes. Notably, even if financial incentives encourage a doctor to prescribe a biosimilar, psychological assumptions may cause a patient to experience negative physical symptoms tied to misperceptions pursuant to a “nocebo effect.”<sup>24</sup> Although such effects can also exist with generics, they may be exacerbated with biosimilars given that biosimilars tend to treat more serious diseases and conditions, such that patients may be particularly attuned to anticipate problems. Understanding and addressing the nocebo effect is essential because it can stymie effective use of biosimilars, especially when such effects are mistakenly attributed to the biosimilar as opposed to a negative mindset.<sup>25</sup> Addressing the nocebo effect is admittedly difficult because not all doctors recognize the

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18. *E.g.*, Makruvet, *supra* note 6, at 4 (noting that biologics are usually administered in a hospital or outpatient facility because they are not in pill format); Dana P. Goldman & Tomas J. Philipson, *Biosimilars Competition Helps Patients More than Generic Competition*, STAT (Oct. 8, 2021), <https://www.statnews.com/2021/10/08/biosimilars-competition-helps-patients-more-than-generic-competition> (noting that biosimilars are typically injected in a doctor’s office); *see also infra* note 58 and accompanying text.

19. *See* discussion *infra* Section I.A.2.

20. *See* discussion *infra* Section III.A.1.

21. *See* discussion *infra* Section III.B.3.

22. *See* discussion *infra* Section I.A.

23. *See* discussion *infra* Section III.B.1.b.

24. The nocebo effect is similar to the better-known placebo effect; essentially, patients who believe they receive a generic or biosimilar experience negative physical symptoms that may reflect their psychological biases. *See* discussion *infra* Section II.B for additional information.

25. Although it may seem hard to distinguish adverse effects that are due to medication from nocebo effects, studies show a pronounced nocebo effect with biosimilars, even if patients might perceive them to be due to medication. *See* discussion *infra* Section I.C.2.

phenomenon.<sup>26</sup> Patients report greater side effects when they are told they received a biosimilar versus blinded studies when they do not know whether they received a biosimilar or originator biologic. This result is compelling evidence that perception can cause alleged side effects.<sup>27</sup> Moreover, doctors that recognize a need to combat the nocebo effect must still recognize their own potential bias and modify their patient communications to combat the effect.<sup>28</sup> Although challenging, initial studies show that reducing the nocebo effect is possible and is therefore an important part of addressing biosimilar use.<sup>29</sup>

This Article proceeds in four Parts. Part I provides background to biologics and cognitive biases that is essential to understanding the overall argument that cognitive biases are impeding greater use of biosimilars in the United States. Section I.A provides background concerning the science behind biologics, the process for approving biologics for sale and distribution, and the costs of originator biologics versus biosimilars. Section I.B then introduces cognitive biases that shape how all information is perceived. Section I.C explains how doctors and patients have biases against generics, which provides a foundation for their biases against biosimilars. Importantly, this Section reveals that although doctors state that they know generics are in fact safe and effective, a significant number do not prefer to prescribe them, thus revealing an unprincipled bias against generics.<sup>30</sup>

Part II illustrates the extent to which doctor and patient biases against biosimilars are stronger than their biases against generics. Because biosimilars have only recently been marketed in the United States, this Part draws upon studies worldwide to document these biases. This Part concludes with an explanation of how these biases economically favor manufacturers of originator biologics who are then motivated to engage in actions that perpetuate the biases.

Part III explains how biases against biosimilars are perpetuated in the United States. Section III.A explains how unique aspects of U.S. law and policy perpetuate biases by unduly emphasizing that biosimilars are different from the corresponding originator biologics. This Section demonstrates that the unique U.S. regulatory designation of an interchangeable biologic needlessly suggests an important difference, given that there is no

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26. See, e.g., Lieven Pouillon, Silvio Danese, Alisa Hart, Gionata Fiorino, Marjorie Argollo, Carlo Selmi, Carmelo Carlo-Stella, Damien Loeuille, Antonio Costanzo, Anthony Lopez, Elena Vegni, Simona Radice, Daniela Gilardi, Marie Socha, Maria Fazio, Marien Gonzalez-Lorenzo, Stefanos Bonovas, Fernando Magro, & Laurent Peyrin-Biroulet, *Consensus Report: Clinical Recommendations for the Prevention and Management of the Nocebo Effect in Biosimilar-Treated IBD Patients*, 49 ALIMENT PHARMACOLOGY & THERAPEUTICS 1181, 1181 (2019) (noting nocebo effect is under-recognized).

27. See discussion *infra* Section II.B.

28. See Joan O'Callaghan, Margaret Bermingham, Maurice Leonard, Frank Hallinan, J. Michael Morris, Una Moore, & Brendan T. Griffin, 88 REGUL. TOXICOLOGY & PHARMACOLOGY 252, 255–57 (2017).

29. See discussion *infra* Section IV.B.2.

30. See discussion *infra* Section I.C.1.

similar designation for generics or for biosimilars approved by other countries. Along similar lines, the United States has required different nonproprietary (not brand) names<sup>31</sup> for biosimilars. This requirement suggests a needless distinction because generics share the identical nonproprietary name with their brand counterparts and biosimilars approved by other countries typically share the identical nonproprietary name. Section III.B explains how some originator biologic manufacturers have capitalized on nonproprietary name differences—and on fabricated distinctions and fear-mongering—to suggest that biosimilars are not safe. Section III.C concludes by explaining why marketing is especially effective due to common cognitive biases that all individuals have.<sup>32</sup>

Part IV then turns to the implications of current biases against biosimilars. Section IV.A acknowledges the difficulties of changing biases, but also notes that structural changes can nonetheless nudge individuals towards desired action. Section IV.B then proposes a multipronged approach to minimize the existence, or at least the impact, of biosimilar bias. This Section suggests changing structural impediments and improving education of doctors and patients in light of biases, as well as fixing financial incentives to favor biosimilars in a manner that has had success with generics.

## I. BACKGROUND

Understanding how biologics differ from traditional drugs is necessary to appreciate why doctor and patient biases against biosimilars are unjustified. This Part first explains the underlying science behind biologics and how it differs from the science behind generics. Next, this Part explains how biosimilars are approved and distributed. Last, this Part explains how the bias against generics may fuel biases against newer biosimilars.

### A. What Are Biologics?

#### 1. Introduction to Biologics and Their Distinction from Traditional Drugs

Because biologics are often the result of modern biotechnology and can be tailored in a manner unlike traditional “small molecule” (i.e., smaller than a biologic) drugs, they can offer important treatments

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31. A nonproprietary name is one that applies to all drugs with the same active ingredient even if they are sold under different brand names. See Karan B. Thakkar & Gauri Billa, *The Concept of: Generic Drugs and Patented Drugs vs. Brand Name Drugs and Non-Proprietary (Generic) Name Drugs*, 4 FRONTIERS IN PHARM. 113, 113 (2013). For example, ibuprofen is the nonproprietary name that is sold under brand names Advil or Motrin and is alternatively sold as a generic store brand, for example as Walgreens ibuprofen or CVS ibuprofen.

32. See discussion *infra* Section III.C; see also Hillel P. Cohen & Dorothy McCabe, *Combating Misinformation on Biosimilars and Preparing the Market for Them is Costing the U.S. Billions*, STAT (June 19, 2019), <https://www.statnews.com/2019/06/19/misinformation-biosimilars-market-preparation> (providing examples of marketing misinformation).



that are targeted to a gene or protein.<sup>33</sup> Biologics can provide revolutionary care for severe and chronic conditions; the importance of biologics is underscored by the fact that they account for half of the drug market in oncology.<sup>34</sup> One type of biologic is a monoclonal antibody, which is designed to provide targeted treatment for a variety of conditions including cancer, autoimmune diseases, and COVID-19.<sup>35</sup> Regeneron, for example, treats COVID-19 with a combination of two different monoclonal antibodies.<sup>36</sup>

There are two types of biologics—an originator biologic and a biosimilar. The originator biologic is the biologic first approved by the FDA to treat a particular condition.<sup>37</sup> A biosimilar is a subsequently approved biologic that is highly similar to an originator and, although not identical, close enough to be used in lieu of the originator at a lower cost.<sup>38</sup> Since 2010, the United States has provided an abbreviated process for approving biosimilars to promote market entry of these lower cost biologics—similar to the abbreviated procedure used for approving generics as lower cost versions of traditional drugs.<sup>39</sup>

All biologics, including biosimilars, are made from living cells and are generally injected or infused because, unlike traditional drugs, they are too big to fit in a pill or tablet.<sup>40</sup> Whereas traditional drugs, including generic drugs, are essentially chemical compounds that are easily mass-produced, biologics are complicated to create because cell lines are known to be unpredictable, and they must be produced in limited quantities under highly sensitive conditions.<sup>41</sup> A traditional drug is created by a predictable

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33. E.g., Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, 1 BIOTECH. HEALTHCARE 24, 24, 26, 28 (2004).

34. E.g., Eva Rahman Kabir, Shannon Sherwin Moreino, & Mohammad Kawsar Sharif Siam, *The Breakthrough of Biosimilars: A Twist in the Narrative*, 9 BIOMOLECULES 410, 410, 9 BIOMOLECULES 1, 1 (2019); Sofia Konstantinidou, Angeliki Papaspiliou, & Eleni Kokkotou, *Current and Future Roles of Biosimilars in Oncology Practice*, 19 ONCOLOGY LETTERS 45, 45 (2020).

35. E.g., Huy X. Ngo & Sylvie Garneau-Tsodikova, *What Are the Drugs of the Future?*, 9 MEDCHEMCOMM. 757, 758 (2018); *What are Monoclonal Antibodies and How Do They Work?*, AM.'S BIOPHARMACEUTICAL COS., <https://innovation.org/en/diseases/infectious/coronavirus/how-mono-clonal-antibodies-work> (last updated Aug. 2021).

36. E.g., D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, B.J. Musser, Y. Soo, D. Rofail, J. Im, C. Perry, C. Pan, R. Hosain, A. Mahmood, J.D. Davis, K.C. Turner, A.T. Hooper, J.D. Hamilton, A. Baum, C.A. Kyratsous, Y. Kim, A. Cook, W. Kampman, A. Kohli, Y. Sachdeva, X. Graber, B. Kowal, T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, & G.D. Yancopoulos, *REGN-COV2, A Neutralizing Antibody Cocktail, in Outpatients with COVID-19*, 384 NEW ENG. J. MED 238, 238 (2020).

37. See generally *Biosimilar and Interchangeable Products*, FDA (Oct. 23, 2017), <http://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>.

38. See 42 U.S.C. § 262(i); see also *Biosimilar and Interchangeable Biologics: More Treatment Choices*, FDA (Oct. 12, 2021), <https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices> (stating that biosimilars have no clinically meaningful differences from comparable original biologics).

39. This pathway was enacted as part of the Affordable Care Act. 42 U.S.C. § 18001. As with the generic approval process, biosimilar approval cannot happen until after a certain term of regulatory exclusivity for the originator. However, the exclusivity period for biosimilars is more than twice as long as that for generic drugs—twelve years instead of five. 21 U.S.C. § 355(j)(5)(B)(iv); 42 U.S.C. § 262(k)(7)(A).

40. E.g., Markuvet, *supra* note 6, at 4.

41. *Id.*

chemical process that can be reverse engineered from the drug.<sup>42</sup> The chemical process can guarantee identical results at low cost, enabling companies to cheaply create generic versions of brand drugs. The process for creating a biologic is complex and expensive; a generic drug may cost \$1–\$5 million to develop, while a biosimilar may cost \$250 million.<sup>43</sup> Moreover, the process for making a biologic is generally a trade secret, making it especially hard to manufacture a biosimilar.<sup>44</sup> Even when the process used is the same, there may be differences between batches.<sup>45</sup> In other words, even the originator biologic manufacturer may not get identical results each time.<sup>46</sup>

While biologics can provide powerful treatments, their strength can result in immune reactions that do not exist with traditional drugs. A biologic drug can be perceived as a foreign invader by the body's immune system, prompting an immune response.<sup>47</sup> This problem is unique to biologics and does not occur with traditional drugs because biologics are much larger than traditional drugs and are synthesized differently in the body.<sup>48</sup> Immune reactions are a potential complication for all biologics and can result in serious adverse effects when they arise.<sup>49</sup>

## 2. Biologics Approval and Distribution

Although biologics involve more complexity and sensitivity to manufacture, distribute, and administer than traditional drugs, it does not follow that it is unsafe for manufacturers to create biosimilars of biologics. With increasing technological development and greater scientific certainty, countries have increasingly initiated streamlined regulatory procedures to approve lower cost biosimilars.<sup>50</sup> The streamlined regulatory

42. See Arvind K. Bansal & Vishal Koradia, *The Role of Reverse Engineering in the Development of Generic Formulations*, 29 PHARM. TECH. 50, 50, 54 (2005).

43. See FTC, *Preface to EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION* iii (2009); Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 470–71 (2013).

44. See Price & Rai, *supra* note 17, at 1028.

45. See Rahman Kabir et al., *supra* note 34, at 1, 2, 9.

46. See Arnold G. Vulto & Orlando A. Jaquez, *The Process Defines the Product: What Really Matters in Biosimilar Design and Production?*, 56 RHEUMATOLOGY 14, 15 (2017); Jill Coghlan, Hongliang He, & Anna S. Schwendeman, *Overview of Humira Biosimilars: Current European Landscape and Future Implications*, 110 J. PHARM. SCI. 1572, 1574 (2021); Fernando de Mora, Alejandro Balsa, María Cornide-Santos, Jose-Manuel Carrascosa, Sara Marsal, Javier P. Gisbert, Miguel-Angel Abad, Rafael F. Duarte, Michael Wiechmann, & Rafael Martínez, *Biosimilar and Interchangeable: Inseparable Scientific Concepts?*, 85 BRITISH J. CLINICAL PHARMACOLOGY 2460, 2460 (2019) (noting that even different batches of the original reference biologic are not identical to each other).

47. See J.M. Carrascosa, *Immunogenicity in Biologic Therapy: Implications for Dermatology*, 104 ACTAS Dermo-Sifiligráficas 471, 471 (2013).

48. See Alison Smith, Hugh Manoli, Stacey Jaw, Kimberley Frutoz, Alan L. Epstein, Leslie A. Khawli, & Frank-Peter Theil, *Unraveling the Effect of Immunogenicity on the PK/PD, Efficacy, and Safety of Therapeutic Proteins*, 2016 J. IMMUNOLOGY RSCH. 1, 1 (2016).

49. E.g., David A. Khan, *Hypersensitivity and Immunologic Reactions to Biologics: Opportunities for the Allergist*, 117 ANNALS ALLERGY ASTHMA & IMMUNOLOGY 115, 115 (2016).

50. E.g., Hye-Na Kang, Robin Thorpe, & Ivana Knezevic, *The Regulatory Landscape of Biosimilars: WHO Efforts and Progress Made from 2009 to 2019*, 65 BIOLOGICALS 1, 3 (2020) (noting that the European Union was the first to provide guidelines and since then, a number of countries have guidelines in place).

process provides cost savings because the shortened approval process is less expensive than the lengthy process required for the originator biologic.<sup>51</sup> Notably, the regulatory procedure for biosimilar approval requires substantially more evidence for approval than generics to account for the scientific complexity of biologics.<sup>52</sup> A generic is chemically equivalent to its corollary drug, meaning that a proposed manufacturer of a generic can show “bioequivalence”<sup>53</sup> through routine studies; if a drug is bioequivalent, the FDA infers that the generic will be as safe and effective as its corollary brand drug.<sup>54</sup> A biosimilar, in contrast, scientifically cannot be identical.<sup>55</sup> Accordingly, the regulatory pathway for biosimilars uses the “highly similar” standard in conjunction with a requirement that there be “no clinically meaningful differences” in terms of safety, purity, and potency, even though there may be differences in clinically inactive components.<sup>56</sup> These standards are roughly parallel to the FDA requirement that generic drugs have the same active ingredient, strength, and route of administration for the same intended use.<sup>57</sup>

The U.S. biosimilar approval pathway creates a distinction among different types of biosimilars dispensed at the pharmacy (as opposed to those infused in health-care provider settings) that does not exist with generics. Currently, most biosimilars are dispensed from health-care providers rather than pharmacies.<sup>58</sup> Unlike generic drugs that can be easily

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51. See Blackstone & Joseph, *supra* note 43, at 470–71, 473 (noting the cost to develop a new biologic was \$1.9 billion compared to \$250 million for biosimilar development).

52. E.g., Stacy Elder Dalpoas, Mariana Socal, Celia Proctor, & Kenneth M. Shermock, *Barriers to Biosimilar Utilization in the United States*, 77 AM. J. HEALTH-SYS. PHARMACISTS 2006, 2008 (2020); see also Thomas J. Moore, Morgane C. Mouslim, Jenna L. Blunt, G. Caleb Alexander, & Kenneth M. Shermock, *Assessment of Availability, Clinical Testing, and US Food and Drug Administration Review of Biosimilar Biologic Products*, 181 J. AM. MED. ASSOC. INTERN. MED. 52, 58 (2021) (noting that approval process for biosimilars may be as rigorous as for originator drugs). The FDA will typically require tests to show it has the same biological activity and purity as well as the same underlying skeletal structure. See U.S. DEP’T HEALTH & HUM. SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH. (CDER), & CTR. FOR BIOLOGICS EVALUATION & RSCH. (CBER), SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY 3–4, 10–11 (2015).

53. E.g., Shein-Chung Chow, *Bioequivalence in Drug Development*, 6 WILEY INTERDISC. REV. COMPUTATIONAL STAT. 304, 304–05 (2014) (explaining bioequivalence refers to similar absorption in the blood).

54. 21 U.S.C. § 355(j)(2)(A).

55. See Celia Lu & Elsen C. Jacob, *Biosimilars: Not Simply Generics*, 44 U.S. PHARMACIST 36, 38 (2019); see also Jonathan Kay, *Are There Benefits and Risks to Biosimilars from a Patient Perspective?*, 45 RHEUMATIC DISEASE CLINIC N. AM. 465, 466 (2019) (noting that a biosimilar is similar to another batch of the originator biologic albeit by a different manufacturer); *supra* notes 46–47 and accompanying text (discussing differences between batches).

56. See 21 U.S.C. § 262(i)(2)(A).

57. See *Generic Drugs: Questions & Answers*, FDA, <https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers#q1> (last visited Mar. 16, 2021).

58. E.g., SAYANTAN NIYOGI, NICHOLAS ADOLPH, & ARTEM PASHCHINSKIY, IQVIA, *BIOSIMILARS IN THE U.S.: REIMBURSEMENT AND IMPACTS TO UPTAKE 3* (2021) (noting that except for insulins and anticipated tumor necrosis factor (TNF) inhibitors, most approved biosimilars are not available at pharmacies); BRILL, *supra* note 6, at 5 (noting most biologics administered by physicians and all biosimilars covered by Medicare are administered by physicians under Part B); Jeff Baldetti, *What’s Next for the Biosimilars Market in the U.S.?*, MANAGED HEALTHCARE EXEC. (Nov. 22, 2021), <https://www.managedhealthcareexecutive.com/view/what-s-next-for-the-biosimilars-market-in-the->

substituted at a pharmacy, only biosimilars that meet additional requirements to be classified as interchangeable can be substituted at a pharmacy, despite the fact that every biosimilar is highly similar to the originator biologic.<sup>59</sup> The interchangeable designation is only given to a biosimilar that is supported by additional data showing that any risks in terms of safety or diminished efficacy associated with switching between the originator and the biosimilar is no greater than not switching.<sup>60</sup>

So far, there are only two biosimilars approved as interchangeable in the United States and both approvals are recent. The first approval was in July 2021 for an insulin product sold under the brand name Semglee; however, despite its status as a biosimilar, Semglee's list price of \$100 per vial is still high.<sup>61</sup> In October 2021 the FDA approved Cyltezo as the first interchangeable biosimilar to Humira for inflammatory diseases.<sup>62</sup> The impact of this interchangeable on lowering prices may be modest. Although Humira is widely used, Humira's manufacturer, AbbVie, has negotiated settlements with companies so that no biosimilars, including the recently approved interchangeable Cyltezo, can be sold until 2023.<sup>63</sup> Moreover, by then, these biosimilars still may not have an impact if patients prefer newer, higher concentration versions over approved biosimilars of the original, lower concentration Humira.<sup>64</sup> The newer concentration of

u-s- (stating that biosimilars have predominantly been administered by health-care providers, with the interchangeable insulin biosimilar being the first biosimilar with a predominant retail focus).

59. 42 U.S.C. § 262(i)(3) (permitting biosimilar substitution without the intervention of the health-care provider who prescribed the comparable product).

60. *See id.* § 262(k)(4)(B).

61. *See* Joshua Cohen, *Approval of First Interchangeable Biosimilar, Semglee, is Sign of An Improving U.S. Biosimilars Market, Despite Challenges*, FORBES (Aug. 1, 2021, 1:43 PM); Joseph Walker, *FDA Lets Pharmacies Substitute Inulin With Knockoff Product, in First for a Biologic Drug*, WALL ST. J. (July 29, 2021, 4:09 PM), <https://www.wsj.com/articles/fda-lets-pharmacies-substitute-branded-insulin-with-knockoff-product-in-first-for-a-biologic-drug-11627589200>.

62. *See FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira*, FDA (Oct. 18, 2021), <https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira>. There is another company currently seeking interchangeability status for its biosimilar while also battling AbbVie patents rather than settling with AbbVie to launch in 2023 as many other companies have done. *See* Tony Hagen, *FDA Grants Interchangeable Status for Boehringer Ingelheim's Adalimumab Biosimilar (Cyltezo)*, AM. J. MANAGED CARE: THE CTR. FOR BIOSIMILARS (Oct. 15, 2021), <https://www.centerforbiosimilars.com/view/fda-grants-interchangeable-status-for-boehringer-ingelheim-s-adalimumab-biosimilar-cyltezo->. Other Humira biosimilars with interchangeable status are also expected from Pfizer (Abrilada) and Amgen (Amjevita). Tony Hagen, *Biosimilar Interchangeability: What's in a Name?*, AJMC: THE CTR. FOR BIOSIMILARS (Nov. 11, 2021), <https://www.ajmc.com/view/biosimilar-interchangeability-what-s-in-a-name->; *see also* Tony Hagen, *Twelve Month Court Battle Will Delay Adalimumab Biosimilar Launch for Abvotec*, AJMC: THE CTR. FOR BIOSIMILARS (Oct. 6, 2021), <https://www.centerforbiosimilars.com/view/alvotec-agrees-to-1-year-delay-in-marketing-of-adalimumab-biosimilar>.

63. *See* Jason Laday, *Market Gears Up for Biosimilar Boom in 2023 as Humira Exclusivity Draws to a Close*, HEALIO (June 18, 2021), <https://www.healio.com/news/rheumatology/20210617/market-gears-up-for-biosimilar-boom-in-2023-as-humira-exclusivity-draws-to-a-close>; Stanton Mehr, *Further Dissecting the Launch of Adalimumab Biosimilars in the US*, BIOSIMILARS REV. & REP. (Apr. 21, 2021), <https://biosimilarsrr.com/2021/04/21/further-dissecting-the-launch-of-adalimumab-biosimilars-in-the-us>.

64. Tony Hagen, *Adalimumab Biosimilars Face Product Obsolescence Before Launch*, AJMC: THE CTR. FOR BIOSIMILARS (Jan. 6, 2021) (noting AbbVie has introduced Skyrizi and Rinvoq as high concentration variations of the original formulation), <https://www.centerforbiosimilars.com/view/adalimumab-biosimilars-face-product-obsolence-before-launch>.

Humira is an example of a product enhancement that originator biologics, at times, introduce to maintain market share despite a biosimilar entry into the market.<sup>65</sup>

No other country has a separate regulatory designation for biosimilars that mirrors the U.S. designation of “interchangeable.”<sup>66</sup> Although most countries do not currently have automatic pharmacy substitution of biologics, countries that permit substitution do not impose an additional regulatory designation that requires additional evidence.<sup>67</sup> Australia strongly promotes biosimilar use, including permitting pharmacy substitution of most originator biologics with a biosimilar.<sup>68</sup> In addition, even for countries that do not have automatic substitution at the pharmacy, there have

65. PER TROEIN, MAX NEWTON, & KIRSTIE SCOTT, IQVIA, THE IMPACT OF BIOSIMILAR COMPETITION IN EUROPE 6 (Dec. 2021) (noting that manufacturers of originator biologics have introduced new formulations, dosing changes, and product enhancements to retain market share). Whether the new Humira versions will be successful is unclear because a biosimilar by Alvotech is anticipated to be available in a high-concentration form and is currently seeking interchangeable status. *E.g.*, Ned Pagliarulo, *AbbVie Holds Off Another Humira Challenger with Alvotech Deal*, BIOPHARMADIVE (Mar. 9, 2022), <https://www.biopharmadive.com/news/abbvie-alvotech-humira-biosimilar-settlement-launch/620100/>.

66. See Anita Afzali, Daniel Furtner, Richard Melsheimer, & Philip J. Molloy, *The Automatic Substitution of Biosimilars: Definitions of Interchangeability are not Interchangeable*, 38 ADVANCES THERAPY 2077, 2078–81 (2021). In other countries, the term “interchangeable” refers to doctors considering biosimilars to be equivalent to the originator and thus, using the biosimilar in lieu of the originator. *See id.* at 2081 (noting that Brazil and Japan consider this term to refer to a matter of clinical practice); *see also* EUR. MEDS. AGENCY & EUR. COMM’N, BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS 29 (2019) (noting that the term “interchangeability” refers to the expectation of using a different medicine that yields the same clinical effect and recognizing that the practice is not governed by the European Medicines Agency, but at the national level); Pekka Kurki, Leon van Aerts, Elena Wolff-Holz, Thijs Giezen, Venke Skibeli, & Martina Weise, *Interchangeability of Biosimilars: A European Perspective*, 31 BIODRUGS 83, 88 (2017).

67. See Evelien Moorkens, Arnold G. Vulto, Isabelle Huys, Pieter Dylst, Brian Godman, Simon Keuerleber, Barbara Claus, Maria Dimitrova, Guenka Petrova, Ljiljana Sovic-Brkicic, Juraj Slaby, Robin Sebesta, Ott Lauius, Allan Karr, Morgane Beck, Jaana E. Martikainen, Gisbert W. Selke, Susan Spillane, Laura McCullagh, Gianluca Trifiro, Patricia Vella Bonanno, Asbjorn Mack, Antra Fogege, Anita Viksna, Magdalena Wladysiuk, Helder Mota-Filipe, Dmitry Mehkov, Marija Kalaba, Simona Mencej Bedrac, Jurij Furst, Corrine Zara, Peter Skiold, Einar Magnuson, & Steven Simoens, *Policies for Biosimilar Uptake in Europe: An Overview*, PLOS ONE, Dec. 2017, at 9; Cécile Rémuzat, Anna Kapuśniak, Aleksandra Caban, Dan Ionescu, Guerric Radière, Cyril Mendoza, & Mondher Toumi, *Supply-Side and Demand-Side Policies for Biosimilars: An Overview in 10 European Member States*, 5 J. MKT. ACCESS & HEALTH POL’Y 1, 8 (2017) [hereinafter Rémuzat, *Supply Side*].

68. See *Biosimilar Awareness Initiative*, AUSTRAL. GOV’T DEP’T OF HEALTH (Feb. 1 2022), <https://www1.health.gov.au/internet/main/publishing.nsf/Content/biosimilar-awareness-initiative> (announcing Australia’s promotion of biosimilar use). There are currently eight biosimilars approved for substitution at Australian pharmacies, including biosimilars to Neupogen, Remicade, Enbrel, and Rituximab. *See Biosimilars in Australia — A-Flagging and Sustainability*, GENERICS & BIOSIMILAR INITIATIVE (Jan. 8, 2021), <https://www.gabionline.net/Biosimilars/General/Biosimilars-in-Australia-a-flagging-and-sustainability>; *Which Biosimilar Medicines are Available in Australia?*, AUSTRAL. GOV’T DEP’T OF HEALTH (Feb. 1, 2022), <https://www1.health.gov.au/internet/main/publishing.nsf/Content/biosimilar-which-medicines-are-available-in-australia>. Australia’s promotion of biosimilar substitution at the pharmacy occurs in a different manner than that in the United States because the Australian regulatory agency that reviews biosimilars does not make the substitution determination. *See* Duncan Longstaff, *Switching from Biologic to Biosimilar: Australia’s Unique Approach* (May 28, 2020), <https://www.spruson.com/patents/switching-from-biologic-to-biosimilar-australias-unique-approach>. Instead, the Australian agency that reviews drug coverage as well as pharmacy substitution, in a process called “a-flagging,” makes the determination. *Id.* For an a-flagged biologic, unless the doctor has checked “substitution not permitted” on the prescription, the prescription may be substituted with a biosimilar.

been somewhat equivalent policies to promote biosimilar use, such as considering biosimilars to be medically interchangeable, mandating use of some or all lower cost biosimilars, setting quotas, and using national purchasing policy to purchase the least expensive biologic, typically a biosimilar.<sup>69</sup>

Policies that mandate biosimilar use may be more effective than pharmacy substitution for increasing biosimilar use because most biologics are only provided in health-care settings by intravenous infusion under the supervision of a health-care provider.<sup>70</sup> This is a major difference from generic distribution, which occurs solely at pharmacies where pharmacists are permitted, or even required, to substitute a generic for the brand that the doctor prescribed.<sup>71</sup> This different distribution method for biologics has implications for promoting biosimilars. With generic drugs, the combination of state substitution laws<sup>72</sup> and financial incentives for insurance companies and other payors to promote generic use result in generics constituting over 90% of prescriptions.<sup>73</sup> In contrast, because biologics are generally only available from doctors and current payor incentives do not favor cheaper biosimilars, doctor bias against biosimilars may remain unchecked.<sup>74</sup> Moreover, patients may be more resistant to switching to a biosimilar than a generic of a traditional drug for reasons inapplicable to drugs dispensed in pharmacies. For example, a patient who is switched to a biosimilar may need to travel to a different and potentially inconvenient location for administration, which may also involve support from nurses the patient is not accustomed to.<sup>75</sup>

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69. See INESSS, SAFETY OF SWITCHING BIOLOGICS AND THEIR INTERCHANGEABILITY 35–36, 38 (2020) (noting that Germany and France consider biologic drugs to be interchangeable, while Turkey, Estonia, Poland, and Serbia effectively allow substitution via lack of regulation, and that other countries have quotas or use national purchasing policies); see also discussion *infra* Section IV.A.2.b.i. (discussing Europe); Tony Hagen, *Quebec Makes It Harder to Use Originator Biologics*, AJMC: THE CTR. FOR BIOSIMILARS (May 19, 2021), <https://www.centerforbiosimilars.com/view/quebec-initiates-a-biosimilar-switching-policy> (noting that Quebec became the fourth Canadian province to require switching patients to biosimilars for insurance coverage).

70. See Susan C. Bolge, Helen M. Eldridge, Jennifer H. Lofland, Caitlin Ravin, Philip J. Hart, & Michael P. Ingham, *Patient Experience With Intravenous Biologic Therapies for Ankylosing Spondylitis, Chron's Disease, Psoriatic Arthritis, Psoriasis, Rheumatoid Arthritis, and Ulcerative Colitis*, 2017 PATIENT PREFERENCE ADHERENCE 661, 662 (2017). Biologics are a much larger molecule than traditional drugs and are generally too large to be taken orally. A small number are self-injected and only available at a pharmacy.

71. See Jesse C. Vivian, *Generic-Substitution Laws*, 33 U.S. PHARMACIST 30, 34 (2008).

72. Although most state substitution laws permit the doctor to bar substitution, doctors rarely do so because payor incentives create a large difference in patient co-pays between brand and generic drugs which may prompt patients to raise cost issues with their doctor. See Mariana P. Social, Ge Bai, & Gerard F. Anderson, *Factors Associated with Prescriptions for Branded Medications in the Medicare Part D Program*, 4 J. AM. MED. ASS'N NETWORK OPEN, Mar. 2, 2021, at 9 (finding that only 5% of drugs with available generics are designated to resist substitution in a Medicare sample); see also discussion *infra* Section III.A.1.

73. AAM 2020 ACCESS & SAVINGS, *supra* note 11, at 16.

74. See discussion *infra* Section III.B.2.

75. See *Forced to Switch: Canadian Biosimilar Experience Survey Report*, GASTROINTESTINAL SOCIETY (2020), <https://badgut.org/biosimilars-survey-report-2020> (noting that switching to biosimilar means a new health care team and accessibility issues for patients); Tara Gomes, Daniel

A small, but important, portion of biologics are sold by pharmacists; these biologics treat common conditions like diabetes and arthritis.<sup>76</sup> A pharmacist can substitute a biosimilar for the prescribed biologic if the biosimilar has obtained an interchangeable designation, but only one biosimilar currently on the market has this status (until 2023 when Cyzelto can be marketed).<sup>77</sup> As a result, most patients only receive biosimilars at the pharmacy if a doctor has specifically prescribed a biosimilar. Because the doctor alone decides whether a patient receives an originator biologic versus its biosimilar, there is no mechanism similar to pharmacy substitution of generics to promote biosimilar use, especially given that current payor incentives tend to promote the more expensive originator. When there is more than one biosimilar available, differences between the available biosimilars may impact which is prescribed, besides price. For example, in Europe the most popular version of the commonly used arthritis drug Humira is a citrate-free injection pen that reduces pain at the injection site, but only one of six available biosimilars uses this mechanism.<sup>78</sup>

### 3. The Cost of Biologics

There is a substantial potential for cost savings in the United States if biosimilar use increases nationwide. The most recent RAND study, completed in 2017, estimated savings of \$54 billion over ten years, representing a \$10 billion increase over a 2013 RAND study estimate.<sup>79</sup> In addition, a recent study by the Office of Inspector General found that spending on biologics in 2019 could have decreased by \$84 million.<sup>80</sup> The United

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McCormack, Sophie A. Kitchen, J. Michael Paterson, Muhammad M. Mamdani, Laurie Proulx, Lorraine Bayliss, & Mina Tadrous, *Projected Impact of Biosimilar Substitution Policies on Drug Use and Costs in Ontario, Canada: A Cross-Sectional Time Series Analysis*, 9 CANADIAN MEDICAL ASS'N J. E1055, E1059 (2021) (noting that mandatory switches can lead to increased anxiety for stable patients due to loss of aspects of patient care, such as nurses funded by biologic drug manufacturers).

76. Insulin is unusual because it was not previously approved as a biologic, such that the biosimilar pathway could not be used to expedite biosimilars prior to a March 2020 change to the laws. See *Insulin Gains New Pathway to Increased Competition*, FDA (Mar. 23, 2020), <https://www.fda.gov/news-events/press-announcements/insulin-gains-new-pathway-increased-competition>.

77. See discussion *supra* notes 60–62 and accompanying text.

78. See Coghlan et al., *supra* note 46, at 1574 (noting that this new design was an improvement over earlier models that had larger needles that caused complaints of pain on injection); see also Ariel Dora Stern, Jacqueline L. Chen, Melissa Ouellet, Mark R. Trusheim, Zeid El-Kilani, Amber Jessup, & Ernst R. Berndt, *Biosimilars and Follow-On Products in the United States: Adoption, Prices, and Users*, 40 HEALTH AFF. 989, 997 (2021) (noting that in all product classes, biosimilars are often not available in identical modalities and strengths as the originator biologic and that this may inhibit their adoption).

79. ANDREW W. MULCAHY, JAKUB P. HLÁVKA, & SPECER R. CASE, BIOSIMILAR COST SAVINGS IN THE UNITED STATES: INITIAL EXPERIENCE AND FUTURE POTENTIAL 10 (2017) [hereinafter MULCAHY ET AL., 2017]; ANDREW W. MULCAHY, ZACHARY PREDMORE, & SOREN MATTKE, THE COST SAVINGS POTENTIAL OF BIOSIMILAR DRUGS IN THE UNITED STATES 7 (2014); see also SUZANNE MURIN, MEDICARE PART D AND BENEFICIARIES COULD REALIZE SIGNIFICANT SPENDING REDUCTIONS WITH INCREASED BIOSIMILAR USE 17 (2022) (finding that spending on biosimilars covered by Part D of Medicare could have decreased by \$143 million in 2019 if 90% of biologics were biosimilars).

80. MULCAHY ET AL., 2017, *supra* note 79, at 1 (discussing that at the time of 2017 RAND study, there were only three biosimilars in the U.S. market).

States currently accounts for 60% of biologic sales,<sup>81</sup> yet uses less than 10% of global biosimilars; the United States is primarily spending money on more expensive originator biologics.<sup>82</sup>

The cost of biologics has important health implications for patients. For example, the high cost of the biologic insulin is known to have compromised the health of diabetic patients. Insulin costs nearly doubled from 2012 to 2016,<sup>83</sup> causing some diabetic patients to skip medication doses, resulting in an increased use of medical services<sup>84</sup> or in serious cases, fatalities.<sup>85</sup> Another example exists with degenerative diseases such as arthritis, where lower cost biosimilars could enable patients to start treatment earlier; earlier treatment could prevent irreversible damage, allowing patients to avoid lost income due to disability or unemployment.<sup>86</sup> In Europe, where biosimilars have been available since 2007, the introduction of biosimilars has led to increased use, but reduced costs overall.<sup>87</sup> Lower cost biosimilars could make biologic therapy available for over 1 million additional U.S. patients by 2025.<sup>88</sup> This could be especially important for cancer patients because many cancer treatments are biologics and the high cost of treatment results in noncompliance with treatment regimens, leading to negative clinical outcomes.<sup>89</sup>

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81. BIOSIMILARS FORUM, STRUCTURAL MARKET CHANGES NEEDED IN U.S. TO ACHIEVE COST-SAVINGS FROM BIOSIMILARS 6 (2019); DENIS KENT, SARAH RICKWOOD, & STEFANO DI BIASE, DISRUPTION AND MATURITY: THE NEXT PHASE OF BIOLOGICS 21 (2021). In contrast, Europe accounts for 90% of global biosimilar sales.

82. See Van de Wiele et al., *supra* note 6, at 1203 (discussing how lower U.S. use of biosimilars is due, in part, to patent litigation, which can result in anticompetitive settlements and less biosimilar availability compared to that in Europe; this, in turn, results in higher prices). For example, the widely used arthritis biologic sold as Humira has no competition in the United States until 2023, whereas multiple Humira biosimilars exist in Europe. See Coghlan et al., *supra* note 46, at 1574.

83. Ed Silverman, *Insulin Costs for U.S. Patients Nearly Doubled from 2012 Through 2016, but Usage was Flat*, STAT (Jan. 22, 2019), <https://www.statnews.com/pharmalot/2019/01/22/insulin-drug-prices-diabetes>.

84. See, e.g., Azri Nasruddin, Norsahadah Bachok, Norul Badriah Hassan, & Nyi Nyi Naing, *Insulin Adherence and Associated Factors in Patients with Type 2 Diabetes Mellitus Treated in Klang Primary Health Care Centres*, 28 MALAYS J. MED. SCI. 76, 78 (2021) (discussing adherence in relationship to cost).

85. E.g., Joshua Cohen, *Insulin's Out-of-Pocket Cost Burden to Diabetic Patients Continues to Rise Despite Reduced Net Cost to PBMs*, FORBES (Jan. 5, 2021, 11:17 AM), <https://www.forbes.com/sites/joshuacohen/2021/01/05/insulins-out-of-pocket-cost-burden-to-diabetic-patients-continues-to-rise-despite-reduced-net-costs-to-pbms>; S. Vincent Rajkumar, *The High Cost of Insulin in the United States: An Urgent Call to Action*, 95 MAYO CLINIC PROC. 22, 22 (2020).

86. See, e.g., BIOSIMILARS FORUM, *supra* note 81, at 6; Jeffrey R. Curtis & Jasvinder A. Singh, *The Use of Biologics in Rheumatoid Arthritis: Current and Emerging Paradigms of Care*, 33 CLINICAL THERAPEUTICS 679, 679 (2011); Natlie Boytsov, Xiang Zhang, Kristin A. Evans, & Barbara H. Johnson, *Impact of Plan-Level Access Restrictions on Effectiveness of Biologics Among Patients with Rheumatoid or Psoriatic Arthritis*, PHARMACOECONOMICS 105, 110–11 (2020) (finding that arthritis patients with insurance plans that made access to biologics more cumbersome had lower odds of treatment effectiveness).

87. See BIOSIMILARS FORUM, *supra* note 81, at 5.

88. BIOSIMILARS COUNCIL, BIOSIMILARS IN THE UNITED STATES: PROVIDING MORE PATIENTS GREATER ACCESS TO LIFESAVINGS MEDICINES 1, 5 (2017).

89. Jingyan Yang, Kelly Blinzler, Joshua Lankin, Sapna Vijayakumar, Martine C. Maculaitis, & Ahmed Shelbaya, *Evolving Perceptions, Utilization and Real-World Implementation Experiences of Oncology Monoclonal Antibody Biosimilars in the USA: Perspectives from Both Payers and Physicians*, 36 BIODRUGS 81 (2021).



It is important to consider cost savings from biosimilars in the context of overall cost savings to society. Although biosimilars provide a more modest percent discount from the originator biologic than a generic from its branded counterpart,<sup>90</sup> because biologic treatments typically cost thousands per year per patient, even a relatively small percentage discount still yields substantial savings.<sup>91</sup> This has important implications because the top ten most expensive drugs for Medicare Part B (which covers drugs for patients on Medicare that are typically administered by doctors) are all biologics and account for a large share of Medicare drug spending.<sup>92</sup>

The cost savings from available biosimilars are especially important given that there are many U.S. biologics for which there are no biosimilars available.<sup>93</sup> This point is underscored by the initial price of the recently approved Biogen drug Aduhelm, the first to treat Alzheimer's disease by removing amyloid plaque and the first new Alzheimer's drug since 2003.<sup>94</sup> The drug was initially priced at \$56,000 a year and, based on that, was estimated to cost Medicare more than the annual budget for the Environmental Protection Agency or the National Aeronautics and Space Administration and result in a 50% increase in Medicare spending.<sup>95</sup> Such a price

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90. See MULCAHY ET AL., 2017, *supra* note 79, at 5 (noting that biosimilar prices are 10%–51% less than that of originator biologics); Dana P. Goldman & Tomas J. Philipson, *Biosimilars Competition Helps Patients More Than Generic Competition*, STAT (Oct. 8, 2021), <https://www.statnews.com/2021/10/08/biosimilars-competition-helps-patients-more-than-generic-competition> (noting that biosimilars are on average 30% cheaper, resulting in a savings of about \$665, while on average generics result in a savings of \$86); FDA, *GENERIC COMPETITION AND DRUG PRICES 2–3* (2019) (noting that there is often more generic competition than biosimilar competition because regulatory approval for generics is faster and less costly to obtain; intense competition can lead to discounts of up to 90%).

91. E.g., WINEGARDEN, *supra* note 7, at 4 (finding patient out-of-pocket costs could be reduced by 17% to almost 50% with competition). Moreover, out-of-pocket costs can be very important for the roughly 30% of patients on Medicare without a cap on co-payments. *Id.* at 6.

92. MEDPAC, *A DATA BOOK: HEALTH CARE SPENDING AND THE MEDICARE PROGRAM* 144 (2019); ASPE & DHHS, *Medicare Part B Drugs: Trends in Spending and Utilization, 2006–17*, at 9, 11 (2020).

93. See, e.g., Baldetti, *supra* note 58 (noting that although there are thirty-one FDA-approved biosimilars, only twenty are marketed); see also Holcomb et al., *supra* note 13, at 2 (noting launch date of biosimilars and the seven associated originator biologics); Mario DiPaola, *The State of Biosimilars in the United States*, BIOANALYSIS ZONE (July 15, 2021), [https://www.bioanalysis-zone.com/the-state-of-biosimilars-in-the-united-states\\_spotl\\_biosim\\_covance](https://www.bioanalysis-zone.com/the-state-of-biosimilars-in-the-united-states_spotl_biosim_covance) (reporting on biosimilars approved and marketed as of 2021); *Approval and Launch Date of US Biosimilars – 2021*, GABI (July 5, 2021) <https://www.gabionline.net/reports/approval-and-launch-dates-for-us-biosimilars-2021>.

94. Jon Hamilton, *Cost and Controversy are Limiting Use of New Alzheimer's Drug*, NPR (Nov. 8, 2021, 6:00 AM), <https://www.npr.org/sections/health-shots/2021/11/08/1052833252/cost-and-controversy-are-limiting-use-of-new-alzheimerdrug#:~:text=Aduhelm%20is%20the%20first%20drug,Alzheimer's%20drug%20approved%20since%202003>.

95. Josh Katz, Sarah Kliff, & Margot Sanger-Katz, *New Drug Could Cost the Government as Much as it Spends on NASA*, N.Y. TIMES: THE UPSHOT (June 23, 2021), <https://www.nytimes.com/2021/06/22/upshot/alzheimers-aduhelm-medicare-cost.html>. Even before Medicare decided whether to cover Aduhelm, Medicare premiums increased 15% to potentially cover the drug. Rebecca Pifer, *Biogen's Pricey Alzheimer's Drug Contributes to Major Medicare Premium Hikes*, HEALTHCARE DIVE (Nov. 15, 2021), <https://www.healthcaredive.com/news/biogen-aduhelm-alzheimers-drug-medicare-premium-hikes-2022/610027/>; see also James D. Chambers, Pei-Jung Lin, Sean R. Tunis, & Peter J. Neumann, *Medicare 'Coverage with Evidence Development' For Aducanumab? How Might it Work?*, HEALTH AFFS. (June 30, 2021),

increase was averted after Biogen halved its annual price and Medicare decided to limit coverage to only patients in forthcoming clinical trials to evaluate concerns about Aduhelm's benefits.<sup>96</sup> However, financial exposure for individual patients still looms large since most Medicare patients will not qualify for coverage and private insurance generally does not cover the drug.<sup>97</sup> In addition, Medicare costs for other biologics to treat Alzheimer's currently under review could still be an issue in light of pressure from some members of Congress and patient advocacy groups pushing for coverage.<sup>98</sup>

In addition, unlike the entry of generic drugs into the market, entry of biosimilars into the market can help reduce costs of the originator biologic. After generics enter the market, the original brand generally does not reduce prices and may sometimes even increase prices to profit from consumers who are less price sensitive.<sup>99</sup> This results in the loss of 70%–90% of traditional branded drug sales within the first year after the brand loses exclusivity.<sup>100</sup> In contrast, originator biologics tend to drop 4%–10% per biosimilar entrant<sup>101</sup> although there is great variation and those that only minimally reduce prices may lose market share.<sup>102</sup> Neupogen, a cancer treatment, did not drop its price until after the third biosimilar entrant and even then, only dropped its price 3%–4%. Neupogen lost about half

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<https://www.healthaffairs.org/doi/10.1377/forefront.20210625.284997> (explaining how Medicare makes coverage determinations). The premiums might be reduced now that Medicare has announced limited coverage of Aduhelm. E.g., Rachel Cohrs, *Medicare Premiums Could Decrease "Soon," After Decision on Alzheimer's Drug Aduhelm*, STAT (Mar. 17, 2022), <https://www.statnews.com/2022/03/17/medicare-premiums-decrease-alzheimers/>

96. CMS, *CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease*, CMS.GOV (Apr. 7, 2022), <https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment>.

97. Juliette Cubanski & Tricia Neuman, *FDA's Approval of Biogen's New Alzheimer's Drug Has Huge Cost Implications for Medicare Beneficiaries*, KAISER FAM. FOUND. (June 10, 2021), <https://www.kff.org/medicare/issue-brief/fdas-approval-of-biogens-new-alzheimers-drug-has-huge-cost-implications-for-medicare-and-beneficiaries/>; Hamilton, *supra* note 94.

98. Pam Belluck, *Inside a Campaign to Get Medicare Coverage for a new Alzheimer's Drug*, N.Y. TIMES (Apr. 6, 2022), <https://www.nytimes.com/2022/04/06/health/aduhelm-alzheimers-medicare-patients.html>.

99. See Richard G. Frank & David S. Salkever, *Generic Entry and the Pricing of Pharmaceuticals*, 6 J. ECON. & MGMT. STRATEGY 75, 82–83 (1997); Richard G. Frank, Mahnum Shahzad, William B. Feldman, & Aaron S. Kesselheim, *Biosimilar Competition: Early Learning* 5 (Nat'l Bureau of Econ. Rsch., Working Paper No. 28460, 2021) [hereinafter Frank et al., Working Paper 2021].

100. See Frank et al., Working Paper 2021, *supra* note 99, at 18.

101. See *id.*; see also Alice M. Ellyson & Anirban Basu, *Do Pharmaceutical Prices Rise Anticipating Branded Competition?*, 30 HEALTH ECON. 1070, 1079 (2021) (finding that in the insulin market, originator biologics increased in price before potential biosimilar entry although out-of-pocket costs did not substantially increase despite 300% increases in overall cost).

102. See Frank et al., Working Paper 2021, *supra* note 99, at 18–19; see also *id.* at 14–16 (showing the change in originator share is fairly substantial for most originators after biosimilar entry except for Remicade); Luca Maini, Josh Feng, Thomas Hwang, & Jacob Klimek, *Biosimilar Entry and the Pricing of Biologic Drugs* (Jan. 4, 2021) (unpublished manuscript at 3, 11–12, 23), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3760213](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3760213) (suggesting that originator biologics decrease net price by about 20% to compete with biosimilars); WAYNE WINEGARDEN, PAC. RSCH. INST., *THE BIOSIMILAR OPPORTUNITY: A STATE BREAKDOWN* 18–20 (2019) (discussing price impact to Remicade and Neupogen once biosimilar competitors introduced to market); Stern et al., *supra* note 78, at 997 (noting greater decline in price of originator biologics to more recent biosimilars).

of its sales volume to biosimilars that were launched at prices 16%–48% lower.<sup>103</sup> In contrast, the price of Remicade—which treats a variety of conditions including arthritis, Crohn’s disease, and psoriasis—dropped nearly 15% after the second biosimilar entered and continued to drop after entry of a third biosimilar, such that it ultimately dropped about 40%–50% of its precompetition price, yet maintained a substantial share of the market.<sup>104</sup> Recently, biosimilars have captured market share more rapidly, resulting in steeper price reductions of the originator biologic.<sup>105</sup>

Moreover, even if the originator biologic does not significantly decrease its price after biosimilar entry, the increased price competition typically halts previous annual price increases. Without competition, originator biologics tend to annually increase prices at least 5% per year.<sup>106</sup> However, in some instances, price increases of originator biologics are much more substantial. Humira, a top-selling originator biologic, increased in price by 19% in 2017 and 2018 and by 7% in 2020 and 2021.<sup>107</sup> Without biosimilar competition until 2023, Humira’s price is likely to continue to increase based on past practice, barring intervening changes in state or federal law.<sup>108</sup>

### B. Introduction to Cognitive Biases

This Section explains how all individuals, regardless of education, are susceptible to imperfect processing of information due to cognitive biases, which are essentially mental shortcuts. As will be explained,

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103. See Frank et al., Working Paper 2021, *supra* note 99, at 16.

104. *Id.* at 15 fig.2a. Occasionally the savings are dramatic; AbbVie provided a nearly 80% discount on Humira to remain the exclusive producer in Nordic countries where only the cheapest version of a drug is available to consumers. Coghlan et al., *supra* note 46, at 1580.

105. See Stern et al., *supra* note 79, at 993 (finding that biosimilars entering the market in 2018 or later showed more rapid market share declines for the originator biologic, especially for biosimilars for bevacizumab and trastuzumab); Yang et al., *supra* note 89, at 79 (noting that recently launched oncology biosimilars received 20%–42% uptake within their first year).

106. See Alvaro San-Juan-Rodriguez, Walid F. Gellad, Chester B. Good, & Inmaculada Hernandez, *Trends in List Prices, Net Prices, and Discounts for Originator Biologics Facing Biosimilar Competition*, 2 J. AM. MED. ASS’N NETWORK OPEN, Dec. 2019, at 1/4 (discussing prices of filgastim, pegfilgrastim, infliximab, and insulin glargine). However, for infliximab and insulin glargine, the net, rather than list prices, decreased a couple of years before biosimilar entry due to increases in manufacturer discounts. See *id.* at 2/4–3/4.

107. Christopher Rowland, *Why Price of Humira Keeps Rising Despite FDA Approval of Generic Competition*, WASH. POST (Jan. 8, 2020), [https://www.washingtonpost.com/business/economy/why-humiras-price-keeps-rising-despite-fda-approval-of-generic-competition/2020/01/07/549ed0ce-2e3a-11ea-bcb3-ac6482c4a92f\\_story.html](https://www.washingtonpost.com/business/economy/why-humiras-price-keeps-rising-despite-fda-approval-of-generic-competition/2020/01/07/549ed0ce-2e3a-11ea-bcb3-ac6482c4a92f_story.html) (noting price increases from 2017 through 2020); Sy Mukherjee, *Will AbbVie, Maker of the World’s Best-Selling Drug, Finally Face the Music Over Its Price Hikes?*, FORTUNE (May 19, 2021, 1:24 PM), <https://fortune.com/2021/05/19/abbvie-humira-drug-prices-of-medicine-drugmakers-big-pharma-prescription-price> (noting Humira price increase of 7.4% in 2021). In fact, a 1.4 billion increase in U.S. drug spending was due to an unsupported net price increase for Humira over two years without any increased benefit. DAVID M. RIND, FOLUSO AGBOOLA, DMITRIY NIKITIN, AVERY MCKENNA, NOEMI FLUETSCH, JON CAMPBELL, FRANCESCA BEAUDOIN, & STEVEN D. PEARSON, INST. FOR CLINICAL & ECON. REV., UNSUPPORTED PRICE INCREASE REPORT: UNSUPPORTED PRICE INCREASES OCCURRING IN 2020 ES2–ES3 (2021) (interim report).

108. See Rowland, *supra* note 107; see also Sy Mukherjee, *It’s the New Year, and Pharma Companies are Already Hiking Prices of Popular Drugs*, FORTUNE (Jan. 4, 2021, 1:35 PM), <https://fortune.com/2021/01/04/drug-price-increases-abbvie-humira>.

cognitive biases operate in conjunction with marketing, resulting in illogical biases against biosimilars.<sup>109</sup> Studies repeatedly show that individuals often make decisions without a systematic consideration of evidence.<sup>110</sup> In an information-saturated society, everyone relies on cognitive shortcuts to deal with time-limited situations and ambiguous information.<sup>111</sup> For example, studies show that doctors repeatedly rely on mental shortcuts to develop diagnoses because patients often present symptoms that are not neatly categorized, which creates ambiguity in diagnosis.<sup>112</sup> Although this practice may seem improper, it is consistent with study findings that individuals use mental shortcuts to fill in incomplete information such as symptoms that do not readily fit a category. Similarly, because there are generally no studies comparing new drugs to old drugs, doctors likely rely on a personal rule of thumb, rather than empirical evidence, to prefer either new drugs or old drugs.<sup>113</sup>

These mental shortcuts are highly prevalent and although they have some utility, they can also result in inaccuracies. Studies indicate that mental shortcuts promote psychological well-being in that they help us to feel more in control in the world.<sup>114</sup> Their utility is potentially highlighted by the fact that individuals develop these shortcuts from an early age; studies have found evidence of children relying on mental shortcuts.<sup>115</sup> Although it may seem obvious that shortcuts can be unreliable, we do not consciously realize that we are using them and thus can develop views based on these unreliable shortcuts.<sup>116</sup> Problematically, views can be difficult to modify; studies indicate that it can be challenging to disabuse individuals of views on a variety of topics including politically charged issues such as bans on LGBTQ individuals in the military, theories concerning President Kennedy's assassination, and the safety of vaccines.<sup>117</sup>

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109. See *infra* Section III.B.1.

110. See DANIEL KAHNEMAN, THINKING FAST AND SLOW 89–90 (2011) (discussing cognitive processing as primarily influenced by automatic and subconscious thought).

111. See *id.* at 79–81; see also Ronald Chen & Jon Hanson, *Categorically Biased: The Influence of Knowledge Structures on Law and Legal Theory*, 77 S. CAL. L. REV. 1103, 1128 (2004).

112. E.g., Jessica Mantel, *The Myth of the Independent Physician*, 64 CASE W. RES. L. REV. 455, 480–81 (2013).

113. See *id.* at 483 (noting doctors could be biased towards new drugs as presumably better or, alternatively, older drugs on the presumption that longer use indicates safety).

114. See Jeffrey J. Rachlinski, *The Uncertain Psychological Case for Paternalism*, 97 NW. U. L. REV. 1165, 1172 (2003); Chen & Hanson, *supra* note 111, at 1196.

115. Jonathan Baron, Laura Granato, Mark Spranca, & Eva Teubal, *Decision-Making Biases in Children and Adolescents: Exploratory Studies*, 39 MERRILL-PALMER Q. 22, 23–25, 34–36 (1993) (finding similar decision-making biases in children aged seven to fifteen); Steven Novella, *Developing Cognitive Biases in Young Children*, NEUROLOGICA BLOG (July 19, 2018), <https://theness.com/neurologicablog/index.php/developing-cognitive-biases-in-young-children> (noting how young children utilize mental shortcuts).

116. E.g., Cynthia Ho, *Drugged Out: How Cognitive Biases Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419, 436–37 (2014) [hereinafter *Drugged Out*].

117. E.g., Geoffrey D. Munro, Peter H. Ditto, Lisa K. Lockhart, Angela Fagerlin, Mitchell Gready, & Elizabeth Peterson, *Biased Assimilation of Sociopolitical Arguments: Evaluating the 1996 U.S. Presidential Debate*, 24 BASIC & APPLIED SOC. PSYCH. 15, 16 (2002); Jacqueline R. Meszaros, David A. Asch, Jonathan Baron, John C. Hershey, Howard Kunreuther, & Joanne Schwartz-Buzaglo,

Although there are a variety of theories and terms from different disciplines concerning how mental shortcuts are initially formed on key issues, a common cognitive bias helps explain how current biases about biosimilars developed.<sup>118</sup> In particular, doctor and patient bias against biosimilars may stem from the so-called availability bias, whereby more readily available information is assumed true.<sup>119</sup> An example of availability bias is that upon hearing frequent news reports on murders, individuals may mistakenly believe that death by homicide is more likely than from stomach cancer because that information is more available, when in fact death by stomach cancer is nearly twenty times as likely.<sup>120</sup> In the medical context, although doctors think they believe scientific research over marketing, studies show doctors actually believe marketing—even when it contradicts scientific research.<sup>121</sup> This has important implications for biosimilars given that self-interested companies that sell originator biologics have been spreading skepticism concerning biosimilars for years;<sup>122</sup> especially because studies show that repeated information is often presumed correct even if it is from an unreliable source.<sup>123</sup> Although this may seem counterintuitive, people often remember the content of a message longer than they remember the source of a message.<sup>124</sup>

Moreover, the availability bias can be enhanced by a “framing bias,” pursuant to which people are highly influenced by how an item is explained (i.e., the framing). For example, beef framed as 75% lean is valued more than beef framed as 25% fat, despite being identical.<sup>125</sup> The framing bias stands to have a major impact on the public’s perception of drugs when used in drug advertisements. Originator biologics have been

*Cognitive Processes and the Decisions of Some Parents to Forego Pertussis Vaccination for Their Children*, 49 J. CLINICAL EPIDEMIOLOGY 697, 701–02 (1996) (discussing the decision processes of parents who chose to not vaccinate their children from pertussis and the difficulties in persuading them to reassess their decisions even when presented with data supporting vaccination).

118. Mental short cuts include a “schema” (an intuitive rule regarding people and events) and a “heuristic” (an individual’s personal rule of thumb). Mantel, *supra* note 112, at 477–78, 478 n.97. Some scholars simply refer to these biases as “misinformation” without categorizing whether the information believed is not true. *E.g.*, Lewandowsky et al., *supra* note 15, at 107–08.

119. See KAHNEMAN, *supra* note 110, at 129–32, 137–41; Cynthia M. Ho, *A Dangerous Concoction: Pharmaceutical Marketing, Cognitive Biases, and First Amendment Overprotection*, 94 IND. L. J. 773, 805–06 (2019) [hereinafter *Dangerous Concoction*].

120. See ZIVA KUNDA, SOCIAL COGNITION: MAKING SENSE OF PEOPLE 91 (1999).

121. *E.g.*, *Dangerous Concoction*, *supra* note 119, at 815–16; see also Henk G. Schmidt, Silvia Mamede, Kees van den Berge, Tamara van Gog, Jan L.C.M. van Saase, & Remy M.J.P. Rikers, *Exposure to Media Information About a Disease Can Cause Doctors to Misdiagnose Similar-Looking Clinical Cases*, 89 AM. MED. 285, 289 (2014).

122. See discussion *infra* Section III.B.1.

123. *E.g.*, *Drugged Out*, *supra* note 116, at 444. This phenomenon is called the “illusory truth effect,” and is its own type of cognitive bias. Gordon Pennycook, Tyrone D. Cannon, & David G. Rand, *Prior Exposure Increases Perceived Accuracy of Fake News*, 147 J. EXP. PSYCH. 1865, 1866 (2018); Jonas De Keersmaecker, David Dunning, Gordon Pennycook, David G. Rand, Carmen Sanchez, Christian Unkelbach, & Arne Roets, *Investigating the Robustness of the Illusory Truth Effect Across Individual Differences in Cognitive Ability, Need for Cognitive Closure, and Cognitive Style*, 46 PERSONALITY & SOC. PSYCH. BULL. 211, 212 (2019).

124. *E.g.*, *Drugged Out*, *supra* note 116, at 443–45.

125. Irwin P. Levin & Gary J. Gaeth, *How Consumers Are Affected by the Framing of Attribute Information Before and After Consuming the Product*, 15 J. CONSUMER RES. 374, 374 (1988).

advertised for over a decade before their corresponding biosimilar enters the market and have likely had a major impact on doctors and patients due to the substantial availability and framing in favor of the originator biologics.<sup>126</sup> As a result, doctors could be unnecessarily hesitant to prescribe biosimilars and patients unnecessarily hesitant to take them. Further reinforcing skepticism surrounding biosimilars, some “neutral” patient groups are funded by self-interested biosimilars companies.

Once doctors and patients develop a bias concerning biosimilars, the bias is perpetuated through “confirmation bias,” which a host of studies have shown to exist in individuals.<sup>127</sup> Under the premise of confirmation bias, individuals interpret new information based on existing beliefs and reject inconsistent information.<sup>128</sup> Even scientists, who are trained to consider information analytically, are not immune to the phenomenon. For example, a 2013 study debunked a common belief among scientists that breakfast is important for weight loss and control, finding that many results lacked probative value or reflected bias.<sup>129</sup> Confirmation bias helps explain why not all individuals recognize climate change despite scientists in the field repeatedly confirming its existence; someone who does not recognize climate change will cling to a minority of information and their own personal experience while disregarding overwhelming relevant evidence.<sup>130</sup> While this may seem illogical, as noted earlier, mental processing is often not entirely logical. In fact, studies show that information that is inconsistent with one’s beliefs is more difficult to process and more closely scrutinized and as a result, is less likely to be accepted as true.<sup>131</sup> The impact of confirmation bias is especially prevalent in ambiguous situations; for example, in one classic study, subjects given the same fact scenario reinforced their beliefs either for or against the death penalty after reading the same scenario.<sup>132</sup> Moreover, as will be explained, the psychological power of confirmation bias may help explain why patients experience positive (placebo) physical effects based on inert substances, as well as negative (nocebo) physical effects with active substances.<sup>133</sup>

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126. The separate “anchoring bias” phenomenon refers to people relying more on initial information they receive. Predrag Teovanović, *Individual Differences in Anchoring Effect: Evidence for the Role of Insufficient Adjustment*, 15 EUR. J. PSYCH. 8, 8 (2019).

127. E.g., *Drugged Out*, *supra* note 116, at 438–41.

128. See RICHARD NISBETT & LEE ROSS, HUMAN INFERENCE: STRATEGIES AND SHORTCOMINGS OF SOCIAL JUDGMENT 169 (1980).

129. See generally Andrew W. Brown, Michelle M. Bohan Brown, & David B. Allison, *Belief Beyond the Evidence: Using the Proposed Effect of Breakfast on Obesity to Show Two Practices that Distort Scientific Evidence*, 98 AM. J. CLINICAL NUTRITION 1298, 1298–1301, 1304–06 (2013).

130. See, e.g., Natasha Bertrand, *Why People Don’t Believe in Climate Change*, INSIDER (Nov. 25, 2014, 3:51 PM), <https://www.businessinsider.com/public-religion-report-climate-change-2014-11>.

131. E.g., Lewandowsky et al., *supra* note 15, at 112.

132. Charles G. Lord, Lee Ross, & Mark R. Lepper, *Biased Assimilation and Attitude Polarization: The Effects of Prior Theories on Subsequently Considered Evidence*, 37 J. PERSONALITY & SOC. PSYCH. 2098, 2098 (1979).

133. See discussion *infra* Section I.C.2.

Availability bias and confirmation bias can be a powerful combination and can help explain things that otherwise seem illogical. For example, the initial study arguing that the measles, mumps, and rubella vaccine was linked to autism was published in 1998 but was not retracted for being based on falsified data until 2010; the flawed study was available to the public for more than a decade, amplified by news reports of the findings.<sup>134</sup> Although reviewing scientists noted in 1998 that the study's sample size was small and that the results could not be replicated, the long period prior to retraction likely reinforced belief in the study results that were then difficult to dismantle due to confirmation bias.<sup>135</sup> That people continue to believe, based on cognitive biases, something that has been debunked as fraudulent science suggests that doctors and patients who have been exposed to negative advertisements about biosimilars may continue to view biosimilars negatively. Simply removing biosimilar misinformation is likely inadequate to reverse opinions and promote their use, and even affirmatively correcting biosimilar misinformation might still be insufficient to change biases.

An additional cognitive bias that may contribute to resistance to biosimilars is the conceptually related bias of "loss aversion." Studies indicate that individuals are sensitive to whether information is framed as a loss, rather than a gain.<sup>136</sup> This bias overvalues possible loss compared to possible gain such that possible gain may need to be twice as valuable for people to overcome this bias.<sup>137</sup> An implication of loss aversion is that individuals tend to retain the status quo.<sup>138</sup> This may play a role in patient and doctor resistance to changing from an originator biologic to its equivalent biosimilar, especially if the change is framed as a potential loss in symptom control.<sup>139</sup> Biologics treat serious conditions and are often

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134. Paul Offit, *Wakefield Study Linking MMR Vaccine, Autism Uncovered as Fraud*, HEALIO (Feb. 1, 2011), <https://www.healio.com/news/pediatrics/20120325/wakefield-study-linking-mmr-vaccine-autism-uncovered-as-complete-fraud>; Julia Belluz, *Research Fraud Catalyzed the Anti-Vaccination Movement. Let's Not Repeat History*, VOX, (Mar. 5, 2019, 12:06 PM), <https://www.vox.com/2018/2/27/17057990/andrew-wakefield-vaccines-autism-study>.

135. See Robert T. Chen & Frank DeStefano, *Vaccine Adverse Events; Causal or Coincidental?*, 351 LANCET 611, 611–12 (1998).

136. See Dawn K. Wilson, Robert M. Kaplan, & Lawrence J. Schneiderman, *Framing of Decisions and Selections of Alternatives in Health Care*, 2 SOC. BEH. 51, 51 (1987) (finding individuals more likely to select risky medical options when information is worded positively).

137. See Chris Guthrie, *Prospect Theory, Risk Preference, and the Law*, 97 NW. U. L. REV. 1115, 1119 (2003) ("In fact, the available empirical evidence suggests that losses generally loom at least twice as large as equivalent gains."). A similar concept is the endowment effect which refers to overvaluing owned items. Daniel Kahneman, Jack L. Knetsch, & Richard H. Thaler, *Experimental Tests of the Endowment Effect and the Coase Theorem*, 98 J. POL. ECON. 1325, 1326–28 (1990). In one classic study, subjects that owned a mug valued it twice as much as those who did not own a mug when they were asked what they would pay for it. See *id.* at 1338–39. Arguably endowment effect could apply to overvaluing a prescription to a current drug, although the fact that it exists is a function of loss aversion. See Daniel Kahneman, Jack L. Knetsch, & Richard H. Thaler, *Anomalies: The Endowment Effect, Loss Aversion, and Status Quo Bias*, 5 J. ECON. PERSP. 193, 194 (1991) [hereinafter *Anomalies*].

138. *E.g.*, *Anomalies*, *supra* note 137, at 197–98.

139. Because studies show that people treat the same scenarios differently if they are framed as a loss versus a gain, framing a surgery as an 80% survival rate as opposed to a 20% mortality rate has different outcomes even though the odds are equivalent.

considered superior treatments such that by the time patients are using biologics, they have tried a variety of inferior drugs in an attempt to treat their condition and are primed to avoid loss, leading to overvaluing maintaining current therapy.<sup>140</sup> Resistance to a change to a biosimilar seems especially likely given that studies show a bias for the status quo even when that status quo is suboptimal.<sup>141</sup> Loss aversion bias could explain why patients taking medications that do not fully control arthritis symptoms sometimes are resistant to changing medications.<sup>142</sup>

### C. Bias Against Generics

This Section explains how doctor and consumer biases against generics can be explained by cognitive biases. As discussed in the last Section, cognitive biases influence how we perceive new information such that existing biases against generics likely taint views of biosimilars. A better understanding of how biases against biosimilars, as well as generics, are grounded in common cognitive biases is helpful to ultimately provide realistic proposals to address misconceptions, as discussed in Part IV. Because biosimilars are relatively new and analogous to well-known generics, this Section begins with evidence of misperceptions about generics. In addition, because doctors are presumably more knowledgeable about drugs than patients and can influence patients, this Section first presents evidence of misconceptions among doctors followed by misconceptions among patients.

#### 1. Evidence of Doctor Bias Against Generics

Although most doctors state that generics are safe and effective, the acknowledgement does not translate to their prescribing preferences, reflecting a possible cognitive bias. A 2016 survey of U.S. doctors found that although the vast majority considered generics as effective and safe (89% and 91% respectively), 70% would prefer prescribing brand name traditional drugs over generic drugs.<sup>143</sup> These results can be explained by

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140. See Pamela Walker, *Loss Aversion: Reducing the Risk of New Rx Drugs*, PHARMEXEC (Jan. 8, 2015), <https://www.pharmexec.com/view/loss-aversion-reducing-risk-new-rx-drugs>.

141. See *Anomalies*, *supra* note 137, at 198 (discussing a study examining status quo bias in which a majority of electrical power consumers who experienced unreliable service still preferred to remain with their current service provider rather than choose a new source).

142. See Frederick Wolfe & Kaleb Michaud, *Resistance of Rheumatoid Arthritis Patients to Changing Therapy: Discordance Between Disease Activity and Patients' Treatment Choices*, 56 ARTHRITIS & RHEUMATISM 2135, 2135 (2007); Kelly Gavigan, W. Benjamin Nowell, Mylene S. Serna, Jeffrey L. Stark, Mohamed Yassine, & Jeffrey R. Curtis, *Barriers to Treatment Optimization and Achievement of Patients' Goals: Perspectives from People Living with Rheumatoid Arthritis Enrolled in the Arthritis Power Registry*, 22 ARTHRITIS RES. & THERAPY 7, 16 (2020) (noting that patients are relatively unlikely to change medication unless the change is initiated by a doctor, even if they have high disease activity).

143. Aaron S. Kesselheim, Joshua J. Gagne, Wesley Eddings, Jessica M. Franklin, Kathryn M. Ross, Lisa A. Fulchino, & Eric G. Campbell, *Prevalence and Predictors of Generic Drug Skepticism Among Physicians: Results of a National Survey*, 176 J. AM. MED. ASS'N INTERNAL MED. 845, 845–46 (2016). However, this is better than in prior years. See William H. Shrank, Joshua N. Liberman, Michael A. Fischer, Charmaine Girdish, Troyen A. Brennan, & Niteesh K. Choudhry, *Physician*



“social desirability bias”—where an individual responds to a survey with what they believe to be the socially desirable response instead of their actual belief. Unlike cognitive biases that modify thinking and perceptions, social desirability bias masks what a person truly believes.<sup>144</sup> This bias may cause doctors to prescribe name brand drugs despite knowing that there are rigorous studies showing that generics are not inferior.<sup>145</sup>

An illogical bias against generics is reflected in the fact that virtually all doctors agree that generics are safe and effective yet not as many prescribe them. The bias against generics could be due to availability bias resulting from years of brand drug marketing, which is then perpetuated through confirmation bias and loss aversion bias. As discussed earlier, confirmation bias can lead individuals to discount information that is inconsistent with their views. For example, if an article states that randomized-controlled trials find no problem with a generic drug, yet nonetheless mentions that some experts believe there is a problem, doctors with confirmation bias against generics are likely to focus on the brief mention of the minority of experts who believe there is a problem (similar to the vaccination and autism study). Additionally, doctors swayed by confirmation

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*Perceptions About Generic Drugs*, 45 ANNALS PHARMACOTHERAPY 31, 34 (2011) (finding that roughly half of doctors surveyed had some concern about generic drug quality with about half reporting quality concerns and almost a quarter concerned about efficacy). The increased belief in generic safety could be due to increased use because, at the time of the earlier study, generics were considered underutilized. *Id.* at 31. There is worldwide physician bias against generics with approximately 30% believing generics are less effective. *E.g.*, Sarah Colgan, Kate Faasse, Leslie R. Martin, Melika H. Stephens, Andrew Grey, & Keith J. Petrie, *Perceptions of Generic Medication in the General Population, Doctors and Pharmacists: A Systematic Review*, BMJ OPEN, Nov. 2015, at 3; *see also* Suzanne S. Dunne & Colum P. Dunne, *What Do People Really Think of Generic Medicines? A Systematic Review and Critical Appraisal of Literature on Stakeholder Perceptions of Generic Drugs*, 13 BMC MED. 1, 2 (2015).

144. *E.g.*, Adrian Furnham, *Response Bias, Social Desirability and Dissimulation*, 7 PERSONALITY & INDIVIDUAL DIFFERENCES 385, 385 (1986). However, social desirability bias can be reduced by good survey design. *See* Roger Tourangeau, *Maintaining Respondent Trust and Protecting Their Data*, in THE PALGRAVE HANDBOOK OF SURVEY RESEARCH, at 137–39 (David L. Vannette & Jon A. Krosnick, eds., 2018).

145. *E.g.*, LINDA L. BARRETT, PHYSICIAN ATTITUDES AND PRACTICES REGARDING GENERIC DRUGS 19 (2005) (finding that although a third of doctors at least somewhat felt that “therapeutic failures are a serious problem” with generics, studies do not support this difference); *see also* Rishi J. Desai, Ameet Sarpatwari, Sara Dejene, Nazleen F. Khan, Joyce Lii, James R. Rogers, Sarah K. Dutcher, Saeid Raofi, Justin Bohn, John G. Connolly, Michael A. Fisher, Aaron S. Kesselheim, & Joshua J. Gagne, *Comparative Effectiveness of Generic and Brand Name Medication Use: A Database Study of US Health Insurance Claims*, 16 PLOS MED, Mar. 2019, at 2 (finding equivalent clinical outcomes among patients who used a generic versus the authorized generic product, which are manufactured by brand name producers); R.A. Hansen, J. Qian, R.L. Berg, J.G. Linneman, E. Seoane-Vazquez, S. Dutcher, S. Raofi, C.D. Page, & P.L. Peissig, *Comparison of Outcomes Following a Switch From a Brand to an Authorized Versus Independent Generic Drug*, 103 CLINICAL PHARMACOLOGY & THERAPEUTICS 310, 313 (2018) (finding generics were not clinically worse than authorized generics, which are made by brand name producers); Lamberto Manzoli, Maria Elena Flacco, Sefania Boccia, Elvira D’Andrea, Nikola Panic, Carolina Marzuillo, Roberta Siliquini, Walter Ricciardi, Paolo Villari, & John P. A. Ioannidis, *Generic Versus Brand-Name Drugs Used in Cardiovascular Diseases*, 31 EUR. J. EPIDEMIOLOGY 351, 361 (2016); Aaron Kesselheim, Alexander S. Misono, Joy L. Lee, Margaret R. Stedman, M. Alan Brookhart, Niteesh K. Choudhry, & William H. Shrank, *Clinical Equivalence of Generic and Brand Name Drugs Used in Cardiovascular Disease: A Systemic Review and Meta-Analysis*, 21 J. AM. MED. ASS’N 2514, 2524 (2008) (finding brand name drugs for cardiovascular disease are not better, contrary to substantial number of editorials opposing substitution).

bias may focus on patient reports of adverse reactions to generics of narrow therapeutic index drugs, which have a narrow range of effectiveness and greater potential for toxicity. These doctors might conclude that the patients' anecdotal reports are proof of problems with generics when the patients' negative outcomes are unrelated to generic use.<sup>146</sup> This focus on negative anecdotal reports contrasts with the American Medical Association (AMA) position as well as repeated FDA assurances that all generics, including those with narrow therapeutic indexes, are safe.<sup>147</sup>

## 2. Evidence of Patient Bias Against Generics

Given that doctors are highly educated yet still susceptible to biases, it should not be surprising that studies also reveal patient bias against generics—especially because patient bias is likely tied to a broader consumer bias favoring brand name products<sup>148</sup> and expensive products.<sup>149</sup> Patient bias against generics is more explicit than doctor bias, as reflected by the comment of one study participant who falsely asserted, “Generic medicine is not as effective as . . . the real medicine prescriptions.”<sup>150</sup> Other patients are aware that generics are safe and effective yet nonetheless have implicit biases against generics. This is evidenced by a 40% gap between those that say generics are safe and effective with equivalent side effects versus those that prefer generics in a 2016 study.<sup>151</sup> This finding is similar to prior

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146. Consistent with cognitive bias that favors personal experience over data, doctors may needlessly assume a seizure is “evidence” that the generic is not effective when it could be due to disease progression, as noted by the AMA. VISANTE, UNDERMINING GENERIC DRUG SUBSTITUTION: THE COST OF GENERIC CARVE-OUT LEGISLATION 5 (2008); see also David G. Vossler, Gail D. Anderson, & Jacquelyn Bainbridge, *AES Position Statement on Generic Substitution and Antiepileptic Drugs*, 16 EPILEPSY CURRENTS 209, 210 (2016) (reversing prior position to now favor generic drugs).

147. VISANTE, *supra* note 146, at 5.

148. See Paula Varela, Gastón Ares, Ana Giménez, & Adriana Gámbaro, *Influence of Brand Information on Consumers' Expectations and Liking of Powdered Drinks*, 21 FOOD QUALITY & PREFERENCE 873, 880 (2010) (well-known brand products taste better only when the brand is visible); Jeffrey S. Nevid, *Effects of Brand Labeling on Ratings of Product Quality*, 53 PERCEPTUAL & MOTOR SKILLS 407, 409 (1981) (finding subjects rated Perrier as tasting superior to generically titled seltzer only when label was shown).

149. Liane Schmidt, Vasilisa Skvortsova, Claus Kullen, Bernd Weber, & Hilke Plassmann, *How Context Alters Value: The Brain's Valuation and Affective Regulation System Link Price Cues to Experienced Taste Pleasantness*, SCI. REP. Aug. 2017, at 2 (study participants rated wines as less tasty if they were labeled as cheaper, even when the wines were in fact identical).

150. Keri Sewell, Susan Andreae, Elizabeth Luke, & Monika M. Safford, *Perceptions of and Barriers to Use of Generic Medications in a Rural African American Population, Alabama, 2011*, PREVENTING CHRONIC DISEASE, Aug. 2012, at 2–3.

151. Aaron S. Kesselheim, Joshua J. Gagne, Jessica M. Franklin, Wesley Eddings, Lisa A. Fulchino, Jerry Avorn, & Eric G. Campbell, *Variations in Patients' Perceptions and Use of Generic Drugs: Results of a National Survey*, 31 SOC'Y. GEN. INTERNAL MED. 609, 609 n.5, 611 (2016) (finding that although 90% of patients considered generics effective and safe and 80% stated they had comparable side effects, almost 40% of patients still preferred the brand name drugs).

studies.<sup>152</sup> Further, bias against generics may be more prevalent concerning serious conditions.<sup>153</sup>

Bias against generics could explain the well-documented physical phenomena not tied to active ingredients. Numerous studies have found that patients may experience placebo<sup>154</sup> or nocebo effects<sup>155</sup> based on whether they believe they are taking a brand drug or a generic drug.<sup>156</sup> Although researchers have long recognized that placebo and nocebo effects are tied to expectations and psychology,<sup>157</sup> these effects also provide strong evidence of bias against generics.

Empirical studies demonstrate that placebo and nocebo effects are associated with powerful biases against generics. In one study of subjects who reported frequent headaches, brand-labeled drugs were always perceived as more effective and with fewer side effects than something labeled “generic”—even when the “brand” was inert and the “generic” had the active ingredient (ibuprofen).<sup>158</sup> This study shows a powerful placebo effect with an inert substance and a nocebo effect with an active ingredient. Similarly, in another experiment where subjects were initially given high blood pressure medication and then told they were going to be switched to either a brand or a generic, those receiving the labeled generic experienced higher blood pressure and greater side effects despite receiving an inert substance.<sup>159</sup> In addition, the same placebo and nocebo effects have been

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152. See William H. Shrank, Emily R. Cox, Michael A. Fischer, Jyotsna Mehta, & Niteesh K. Choudhry, *Patients' Perceptions of Generic Medications*, 28 HEALTH AFF. 546, 548–49 (2009) (finding a third of patients believe that brand drugs are more effective and more than a quarter would personally prefer the brand name drug); Amy J. Keenum, Jennifer E. DeVoe, Deena J. Chisolm, & Lorraine S. Wallace, *Generic Medications for You, but Brand-Name Medications for Me*, 8 RSCH. SOC. & ADMIN. PHARMACY 574, 576 (2012) (finding among a sample of female Medicaid patients, nearly two-thirds agreed generics were a better value, but the majority preferred the brand, and about a quarter believed the brand was more effective).

153. See, e.g., Maria João Figueiras, Maria Armanda Cortes, Dália Marcelino, & John Weinman, *Lay Views About Medicines: The Influence of the Illness Label for the Use of Generic Versus Brand*, 25 PSYCH. & HEALTH 1121, 1125–26 (2010) (finding subjects less likely to believe that generic use was appropriate for more serious conditions).

154. For example, it is well known that patients may experience an improvement of symptoms when they expect that to happen, even if given an inert substance (i.e. the placebo effect).

155. Along similar but opposite lines, the nocebo effect results in patients perceiving lack of efficacy or side effects from a generic or even something labeled a generic. See, e.g., Victor Chavarria, João Vian, Círia Pereira, João Data-Franco, Brisa S. Fernandes, Michael Berk, & Seetal Dodd, *The Placebo and Nocebo Phenomena: Their Clinical Management and Impact on Treatment Outcomes*, 39 CLINICAL THERAPEUTICS 477, 478 (2017).

156. Somewhat analogously, studies show individuals perform better with brand name consumer goods that are actually identical. See Aaron M. Garvey, Frank Germann, & Lisa E. Bolton, *Performance Brand Placebos: How Brands Improve Performance and Consumers Take the Credit*, 42 J CONSUMER RSCH. 931, 945 (2016).

157. *Id.*

158. See Kate Fasse & Leslie R. Martin, *Impact of Brand or Generic Labeling on Medication Effectiveness and Side Effects*, 35 HEALTH PSYCH. 187, 188–89 (2016) (finding that, among subjects who report frequent headaches, subjects reported efficacy and fewer side effects with pills labeled “Nurofen” over ones labeled “generic ibuprofen,” whether or not it had an active or inert compound; subjects who received unbranded drugs also reported less efficacy—even if given an active ingredient).

159. Kate Faasse, Tim Cundy, Greg Gamble, & Keith J. Petrie, *The Effect of an Apparent Change to a Branded or Generic Medication on Drug Effectiveness and Side Effects*, 75 PSYCHOSOMATIC

observed with drugs not labeled as brand and generic but with similar characteristics, such as expensive versus cheap<sup>160</sup> or a simple versus complex name, typical of scientific names used for generics.<sup>161</sup> These studies show a bias can not only impact perceptions, but can even manifest physically.<sup>162</sup>

There are also real-life examples of the nocebo effect. For example, there may be a nocebo effect with statins that are frequently prescribed to patients with high blood cholesterol. About 30% of patients discontinue statins due to alleged side effects.<sup>163</sup> However, when patients in clinical trials are unaware of whether they are receiving a statin or an inert placebo, side effects are indistinguishable.<sup>164</sup> Accordingly, it appears that the 30% of patients in the nonclinical setting are experiencing nocebo effects.

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MED. 90, 94 (2013); *see also* Antonella Pollo, Martina Amanzio, Anna Arslanian, Caterina Casadio, Giuliano Maggi, & Fabrizio Benedetti, *Response Expectancies in Placebo Analgesia and Their Clinical Relevance*, 93 PAIN 77, 82–83 (2001) (patients with postoperative pain who were told only that they were given a powerful painkiller that was in fact a placebo needed about one-third less of a stronger additional drug compared to those who knew they had a 50/50 chance of either receiving a placebo or a powerful painkiller); Ulrike Bingel, Vishvarani Wanigasekera, Katja Wiech, Roisin Ni Mhuirheartaigh, Michael C. Lee, Markus Ploner, & Irene Tracey, *The Effect of Treatment Expectation on Drug Efficacy: Imagining the Analgesic Benefit of the Opioid Remifentanyl*, SCI. TRANSLATIONAL MED., Feb. 2011, at 1, 4 (patients perceived a lack of efficacy when told that they are no longer receiving a powerful pain relief medication compared to those not told anything, even though all were receiving the same pain relief).

160. Rebecca L. Waber, Baba Shiv, Ziv Carmon, & Dan Ariely, *Commercial Features of Placebo and Therapeutic Efficacy*, 299 J. AM. MED. ASS'N 1016, 1016–17 (2008) (finding that when subjects were told that they were receiving a more expensive treatment, a pill that costs \$2.50, they experienced greater pain relief than when told they were receiving a heavily discounted treatment, \$.01 per pill, even though all subjects received the identical compound); Alberto J. Espay, Matthew M. Norris, James C. Eliassen, Alok Dwivedi, Matthew S. Smith, Christi Banks, Jane B. Allendorfer, Anthony E. Lang, David E. Fleck, Michael J. Linke, & Jerzy P. Szaflarski, *Placebo Effect of Medication Cost in Parkinson Disease: A Randomized Double-Blind Study*, 84 NEUROLOGY 794, 794 (2015) (patients with Parkinson's were given the same injection with no active ingredient, but perceived efficacy was dramatically different based on alleged cost).

161. *See* Simone Dohle & Michael Siegrist, *Fluency of Pharmaceutical Drug Names Predicts Perceived Hazardousness, Assumed Side Effects and Willingness to Buy*, 19 J. HEALTH PSYCH. 1241, 1248 (2014); Hyunjin Song & Norbert Schwarz, *If it's Difficult to Pronounce it Must be Risky*, 20 PSYCH SCI. 135, 138 (2009); A. Tinnermann, S. Geuter, C. Sprenger, J. Finsterbusch, & C. Büchel, *Interactions Between Brain and Spinal Cord Mediate Value Effects in Nocebo Hyperalgesia*, 358 SCI. 105, 108 (2017) (finding that drugs with a simple name noted as a registered trademark resulted in more pain relief than a product with a more complex name even with no price information disclosed).

162. *See supra* notes 156–59 and accompanying text.

163. *See* Corey K. Bradley, Tracy Y. Wang, Shuang Li, Jennifer G. Robinson, Veronique L. Roger, Anne C. Goldberg, Salim S. Virani, Michael J. Louie, L. Veronica Lee, Eric D. Peterson, & Ann Marie Navar, *Patient-Reported Reasons for Declining or Discontinuing Statin Therapy: Insights from the PALM Registry*, J. AM. HEART ASS'N, Mar. 2019, at 6–9; Kate Faasse & Leslie R. Martin, *The Power of Labeling in Nocebo Effects*, 139 INT'L REV. NEUROBIOLOGY 379, 382 (2018).

164. *See* Ajay Gupta, David Thompson, Andrew Whitehouse, Tim Collier, Bjorn Dahlof, Neil Poulter, Rory Collins, & Peter Sever, *Adverse Events Associated with Unblinded, but not with Blinded, Statin Therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): A Randomized Double-Blind Placebo-Controlled Trial and its Non-Randomized Non-Blind Extension Phase*, 389 LANCET 2473, 2478 (2017); Judith A. Finegold, Charlotte H. Manisty, Ben Goldacre, Anthony J. Barron, & Darrel P. Francis, *What Proportion of Symptomatic Side Effects in Patients Taking Statins are Genuinely Caused by the Drug? Systematic Review of Randomized Placebo-Controlled Trials to Aid Individual Patient Choice*, 21 EUR. J. PREVENTATIVE CARDIOLOGY 464, 467, 471 (2014).

Perceived lack of efficacy could be a misattribution of a natural fluctuation of the disorder or other causes, resulting in nocebo effects.<sup>165</sup>

## II. THE BIAS AGAINST BIOSIMILARS

This Part explains how biases concerning generics extend to biosimilars, making it more challenging for doctors and patients to accept the latter. Although the biases are analogous, understanding the extent of the problem is important in crafting effective solutions. This Part concludes by explaining how originator biologics benefit from this bias, such that they are financially motivated to perpetuate bias as discussed in more detail in Part III.

### A. Evidence of Doctors with Biases Against Biosimilars

Surveys of U.S. doctors indicate a bias against biosimilars despite a majority of doctors now recognizing biosimilars as safe and effective.<sup>166</sup> For example, a 2021 study of about 600 doctors showed that approximately three-quarters consider biosimilars to be at least as safe and effective as their counterpart biologic,<sup>167</sup> but the number of doctors very likely to start a new patient on a biosimilar was less than half.<sup>168</sup> These doctors were resistant to prescribe biosimilars even though a substantial number thought that patient costs would be lower with a biosimilar.<sup>169</sup> Another study with a substantially larger sample size of doctors reported that almost a quarter were unwilling to start new patients on biosimilars even though 83% knew biosimilars have no clinically meaningful difference

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165. See Chavarria et al., *supra* note 155, at 478.

166. Studies from 2017 to 2021 indicate a trend towards an increasing number of doctors viewing biosimilars as safe and effective, but the highest number is still not comparable with a 2016 survey of around 90% of doctors considering generics safe and effective. See Kesselheim et al., *supra* note 151, at 609–11 (survey of doctor views on generics). Whereas the first study of U.S. doctors prescribing biologics found less than half of doctors believed biosimilars to be safe, a survey conducted in 2020 found three-quarters found biosimilars safe. Compare A. Teeple, L.A. Ellis, L. Huff, C. Reynolds, S. Ginsburg, L. Howard, D. Walls, & J. R. Curtis, *Physician Attitudes About Non-Medical Switching to Biosimilars: Results from an Online Physician Survey in the United States*, 35 CURRENT MED. RES. & OPINION 611, 613 fig.2 (2019) (among nearly 300 doctors prescribing biologics, 44% considered biosimilars safe and 42% considered them riskier than generics) with NORC, *supra* note 13, at 3 fig.1 (among 602 doctors prescribing biologics, roughly 75% consider them safe and effective). But see A. Kolbe, A. Kearsley, L. Merchant, E. Temkin, A. Patel, J. Xu, & A. Jessup, *Physician Understanding and Willingness to Prescribe Biosimilars: Findings from a US National Survey*, 35 BIODRUGS 363, 369 (2021) (reporting that a study of 500 health-care professionals with varying prior biosimilar experience found that less than 50% expected biosimilars to perform the same clinically); see also Judith M. Orvos, *US Healthcare Providers (Reluctantly) Prescribe Biosimilars*, MEDPAGE TODAY (June 14, 2021), <https://www.medpagetoday.com/resource-centers/biosimilars-peer-to-peer/us-healthcare-providers-reluctantly-prescribe-biosimilars/3321> (discussing Kolbe study).

167. Seventy-eight percent of doctors considered biosimilars just as safe and 75% considered them just as effective, but more than 10% thought that biosimilars were safer or more effective than the originator drugs. See NORC, *supra* note 13, at 3.

168. *Id.* (showing that there were an additional 39% of physicians that were “somewhat comfortable” with prescribing biosimilars that had been approved by the FDA).

169. *Id.* at 7 fig.7 (finding that 41% of doctors thought that biosimilars would be cheaper most of the time and 44% thought this was true some of the time).

from their related originator biologics.<sup>170</sup> In these studies, as well as older ones, doctors were resistant to prescribing biosimilars despite knowing that they were as safe and effective as the originator biologic.<sup>171</sup> That doctors are most comfortable prescribing biosimilars to new patients (as opposed to patients stable on an originator biologic) suggests a bias against biosimilars. This bias could be sustained by some unique aspects of U.S. biosimilar law and financial coverage in addition to substantial advertising, as discussed in Part III.<sup>172</sup> However, bias is not limited to U.S. doctors.

Similar evidence of doctor bias against biosimilars exists in other countries. A 2018 study of European rheumatologists two years after the first biosimilar was available in their specialty found that the vast majority (over 70%) were satisfied with originator biologics, but less than 40% were satisfied with biosimilars.<sup>173</sup> Most strikingly, a 2014 study of Canadian rheumatologists conducted the same year a biosimilar of originator biologic Remicade was approved in Canada found that only 11% of doctors would choose a biosimilar if cost were not an issue.<sup>174</sup> Familiarity with biosimilars at that time was low—only one-third of surveyed doctors considered themselves familiar.<sup>175</sup> Nonetheless, it is notable that less than 30% of doctors considered drug approval adequate to provide confidence in drug safety and efficacy when regulatory approval demanded such proof,<sup>176</sup> in addition, existing literature showed no problems switching

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170. Allan Gibofsky & Dorothy McCabe, *US Rheumatologists' Beliefs and Knowledge About Biosimilars: A Survey*, 60 RHEUMATOLOGY 896, 898 (2020) (reporting on a survey of over 9,000 rheumatologists); see also Kolbe et al., *supra* note 166, at 367 (noting that 86% would choose the originator biologic over the biosimilar if both were covered).

171. See Simani M. Price, Amie C. O'Donoghue, Lou Rizzo, Saloni Sapru, & Kathryn J. Aikin, *What Influences Healthcare Providers' Prescribing Decisions? Results from a National Survey*, 17 RSCH. SOC. & ADMIN. PHARMACY 1770, 1777 (2021) (survey of 700 primary care physicians and 600 specialists found that less than 40% were at least moderately comfortable prescribing biosimilars, despite knowing what they are, although this does not distinguish between patients new to biologics); Joshua Cohen, *Will 2021 Be Another Break-Through Year for Biosimilars?*, FORBES (Dec. 3, 2020, 9:21 AM), <https://www.forbes.com/sites/joshuacohen/2020/12/03/will-2021-be-another-break-through-year-for-biosimilars> (noting a 2019 study that found that more than 60% of U.S. oncology doctors prefer the brand over biosimilar).

172. See discussion *infra* Part III. Indeed, doctors sometimes note that they would be more likely to switch stable patients to a biosimilar if there were greater cost savings potential. See, e.g., Keith Loria, *Survey: Rheumatologists Still Reluctant to Switch Patients to Biosimilars*, MANAGED HEALTHCARE EXEC. (July 2, 2020), <https://www.managedhealthcareexecutive.com/view/survey-rheumatologist-still-reluctant-to-switch-patients-to-biosimilars> (reporting that in a Cardinal Health survey of 100 rheumatologists, only 11% were likely to prescribe a biosimilar to a stable patient; the rheumatologists cited lack of significant cost benefit and 38% of those surveyed maintained concerns about efficacy of biosimilars); see also Kyle Herndon, Jason Braithwaite, Brittany Berry, & Kathleen Bourget, *Biosimilar Perceptions Among Healthcare Professions and Commercial Medical Benefit Policy Analysis in the United States*, 35 BIODRUGS 103, 108–9 (2021).

173. Casey Zhang, Denise Baldock, & Elizabeth Baynton, *Physician Perceptions of Biologics Versus Their Biosimilar Counterparts in Rheumatology: A Multicountry Study in Europe*, 78 ANNALS RHEUMATIC DISEASE 611, 611 (2019) (evaluating rheumatologists in United Kingdom, France, Italy, Spain, and Germany concerning etanercept, infliximab, and rituximab).

174. David Grabowski, Bradley Henderson, Dennis Lam, Edward C. Keystone, Carter Thorne, Shahin Jamal, Janet Pope, Boulos Harauoi, Daming Lin, & Leigh Revers, *Attitudes Towards Subsequent Entry Biologics/Biosimilars: A Survey of Canadian Rheumatologists*, 34 CLINICAL RHEUMATOLOGY 1427, 1429 (2015).

175. *Id.*

176. *Id.* at 1431 tbl.3.

patients from originator Remicade to biosimilar Remsima.<sup>177</sup> Moreover, a 2016 study of Belgian doctors found that even if the originator was more expensive, 73% preferred it.<sup>178</sup> Notably, this preference was not due to a lack of knowledge about biosimilars—the vast majority had good understanding of the definition of a biosimilar.<sup>179</sup> The disproportionate preference for a more expensive originator biologic despite understanding that biosimilars are highly similar is also consistent with a strong bias against biosimilars.

Bias against biosimilars can also be seen in global studies showing that doctors are generally not comfortable switching stable patients to biosimilars<sup>180</sup> despite empirical studies indicating it is safe.<sup>181</sup> In multiple surveys of doctors, generally no more than 51% of surveyed doctors are comfortable switching a patient to a biosimilar.<sup>182</sup> Cited concerns mirror some of the general concerns about biosimilars, such as concerns that they will be less effective and less safe, as well as that there is inadequate

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177. *Id.* at 1431.

178. See Kati Sarnola, Merja Merikoski, Johanna Jyrkkä, & Katri Hämeen-Anttila, *Physicians' Perceptions of the Uptake of Biosimilars: A Systematic Review*, 10 *BMJ OPEN*, Apr. 2020, at 12 tbl.2.

179. *Id.* (noting that 95% of surveyed doctors self-reported a correct understanding that biosimilars are biologics similar, but not identical to, an originator).

180. *Id.* at 17.

181. See, e.g., Jérôme Avouac, Anna Molto, Vered Abitbol, Adrien Etcheto, Axelle Salcion, Loriane Gutermann, Caroline Klotz, Murial Elhai, Pascal Cohen, Pierre Antoine Soret, Florence Morin, Ornella Conort, Francois Chast, Claire Goulvestre, Claire Le Jeune, Stanislas Chaussade, André Kahan, Christian Roux, Yannick Allanore, & Maxime Dougados, *Systematic Switch from Innovator Infliximab to Biosimilar Infliximab in Inflammatory Chronic Diseases in Daily Clinical Practice: The Experience of Cochin University Hospital Paris, France*, 47 *SEMIN. ARTHRITIS RHEUMATISM* 741, 747 (2018); Edmond-Jean Bernard, Richard N. Fedorak, & Vipul Jairath, *Systematic Review: Non-Medical Switching of Infliximab to CT-P13 in Inflammatory Bowel Disease*, 65 *DIGESTIVE DISEASES & SCI.* 2354, 2368–69 (2019); Kristin K. Jørgensen, Inge C. Olsen, Guro I. Goll, Merete Lorentzen, Nils Bolstad, Espen A. Haavardsholm, Knut E.A. Lundin, Cato Mork, Jørgen Jahnsen, & Tore K Kvien, *Switching from Originator Infliximab to Biosimilar CT-P13 Compared with Maintained Treatment with Originator Infliximab (NOR-SWITCH)*, 389 *LANCET* 2304, 2304 (2017); András Inotai, Christiaan P. J. Prins, Marcell Csanádi, Dinko Vitezic, Catalin Codreanu, & Zoltán Kaló, *Is There a Reason for Concern or is it Just Hype? – A Systematic Literature Review of the Clinical Consequences of Switching from Originator Biologics to Biosimilars*, *EXPERT OP. BIO. THERAPY* 915, 915 (2016); Liese Barbier, Hans C. Ebbers, Paul Declerck, Steven Simoens, Arnold G. Vulto, & Isabelle Huys, *The Efficacy, Safety and Immunogenicity of Reference Biopharmaceuticals and Biosimilars: A Systemic Review*, 108 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 734, 752 (2020); Silvana A. M. Urru, Stefania Spila Alegiani, Anna Guella, Giuseppe Traversa, & Annalisa Campomori, *Safety of Switching Between Rituximab Biosimilars in Onco-Hematology*, *SCI. REP.*, Mar. 2021, at 3; Paul Corens & Matti Aapro, *The Impact of Biosimilars in Supportive Care in Cancer*, 14 *SUPPORTIVE ONCOLOGY* 20, 23–27 (2018) (discussing various studies that show no problems with switching). Switching between biosimilars has also been suggested as safe. See Eduardo Mysler, Valderilio Feijó Azevedo, Silvio Danese, Daniel Alvarez, Noriko Iikuni, Beverly Ingram, Markus Mueller, & Laurent Peyrin-Biroulet, *Biosimilar-to-Biosimilar Switching: What is the Rationale and Current Experience?*, 81 *DRUGS* 1859, 1864–65.

182. Sarnola et al., *supra* note 178, at 17. However, there are differences among specialties, which could reflect lower use of certain biosimilars. See, e.g., Stephen R. Chapman, Raymond W. Fitzpatrick, & Mohammed I. Aladul, *Knowledge, Attitude and Practice of Healthcare Professionals Towards Infliximab and Insulin Glargine Biosimilars: Result of a UK Web-Based Survey*, *BMJ OPEN*, May 2017, at 6 fig.5 (noting differing level of concerns with safety and efficacy of switching to a biosimilar among dermatologists, gastroenterologists, and rheumatologists in a survey of U.K. doctors, with rheumatologists having major concerns for both issues, but no major concerns by gastroenterologists).

clinical data.<sup>183</sup> However, as will be discussed, these concerns also reflect marketing by self-interested originator biologic manufacturers. In addition, doctor bias against biosimilars could reflect confirmation bias that causes them to focus on studies that suggest problems with switching without considering that most of the studies that suggest a problem are observational studies versus the rigorous empirical studies that do not find a problem.<sup>184</sup> Further evidence of an illogical bias against biosimilars is anecdotal; many doctors have no express reason for preferring the originator biologic.<sup>185</sup> Lack of a principled reason is consistent with mental shortcuts based on cognitive biases rather than logical reasoning.

Some doctor bias could be based on a lack of knowledge. For example, a 2019 survey found that the vast majority of U.S. oncologists—almost three-quarters—could not provide a correct definition for biosimilar.<sup>186</sup> In addition, a 2018 survey found that a majority of doctors that prescribe biologics do not prescribe biosimilars because they are not familiar with them.<sup>187</sup> Inadequate knowledge sets the stage for cognitive biases to proliferate to fill in knowledge gaps.<sup>188</sup> It is possible that doctors with existing bias against generics assume that because, unlike generics, biosimilars are not identical to a prior biologic, they should be especially hesitant about prescribing them, resulting in a stronger bias against biosimilars than generics. Bias could be exacerbated by the fact that doctors are not certain that biosimilars would reduce patient out-of-pocket costs given that insurance coverage tends to not favor biosimilars and originator biologic manufacturers often provide discount coupons to patients.<sup>189</sup> This is in stark contrast to the fact that generics are well-known to often be dramatically cheaper than the equivalent brand. Considering that some doctors do not prescribe substantially cheaper generics, bias against prescribing biosimilars that may not be cheaper is not surprising.

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183. Amy Hemmington, Nicola Dalbeth, Paul Jarrett, Alan G. Fraser, Reuben Broom, Peter Browett, & Keith J. Petrie, *Medical Specialists' Attitudes to Prescribing Biosimilars*, 26 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 570, 570–71 (2017).

184. See Inotai et al., *supra* note 181, at 915.

185. See Interview by Matthew Gavidia with Robert Rifkin, M.D., FACP, Med. Oncologist & Hematologist, Rocky Mountain Cancer Ctrs. (Dec. 5, 2020), <https://www.centerforbiosimilars.com/view/robert-rifkin-md-discusses-overcoming-lingering-biosimilar-education-gaps>.

186. Chad Pettit, *The Case for Optimism in the U.S. Biosimilar Market*, BIOSIMILAR DEV. (July 28, 2020), <https://www.biosimilardevelopment.com/doc/the-case-for-optimism-in-the-u-s-biosimilar-market-0001>. Similarly, a 2018 survey of 442 clinicians found 55% were unfamiliar with biosimilars. See ALEX BRILL & CHRISTY ROBINSON, MATRIX GLOB. ADVISORS, BIOSIMILAR SAVINGS OPPORTUNITIES IN THE MEDICAL BENEFIT: A LARGE-EMPLOYER CASE STUDY 3 n.8 (2019).

187. PWC HEALTH RESEARCH INSTITUTE, REGULATORY SPOTLIGHT: GENERIC DRUG PRICING 8 (2018) (reporting that in an April 2018 survey of doctors that already prescribe biologics, 55% said they did not prescribe any biosimilars because they are not familiar with them).

188. See Kendra Cherry, *What is Cognitive Bias?*, VERYWELL MIND (July 19, 2020), <https://www.verywellmind.com/what-is-a-cognitive-bias-2794963>.

189. NORC, *supra* note 13, at 7–8; see also Loria, *supra* note 172 (noting rheumatologists indicate lack of cost savings for patients as an issue for not switching patients to biosimilar).



### B. Evidence of Patient Bias Against Biosimilars

Studies also indicate patient bias against biosimilars. For example, in a 2013 survey of over 3,000 diabetes patients, almost 20% indicated they would be unlikely to or definitely would not use a biosimilar when told it was a lower cost version akin to a generic.<sup>190</sup> Moreover, statements by the subjects seem to reflect bias. For example, some noted that they considered a brand to indicate quality, effectiveness, and trustworthiness, with one noting that because manufacturers spend money on research, that must indicate it is the “best, safest, and fastest” product.<sup>191</sup> One respondent stated, “I would be concerned about quality” for a hypothetical insulin biosimilar.<sup>192</sup>

Although biosimilars are new to the United States, studies of patients in Europe, where biosimilars have been available since 2006, also show patient bias against biosimilars. For example, one study found that the vast majority of German patients treated with an originator biologic for gastrointestinal issues were satisfied while a lower number of patients receiving a biosimilar were satisfied, including differing perceived control of symptoms.<sup>193</sup> As with studies of doctors, patients were biased against biosimilars even if they were more cost-effective.<sup>194</sup> A study of French rheumatology patients revealed that although 99% considered themselves sensitive to medication cost, the vast majority (almost 80%) had some hesitancy to use biosimilars to reduce cost, often due to a misconception that the lower cost meant lower quality.<sup>195</sup>

Express bias against biosimilars seems to align with patients’ willingness to switch from a brand to a biosimilar. In one study, a majority of patients were concerned about quality and roughly 40% were concerned about efficacy, safety, or both if they switched to a biosimilar.<sup>196</sup> A subsequent study found that patients who refused to switch to a biosimilar to

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190. Alasdair R. Wilkins, Manu V. Venkat, Adam S. Brown, Jessica P. Dong, Nina A. Ran, James S. Hirsch, & Kelly L. Close, *Patient Perspectives on Biosimilar Insulin*, 8 J. DIABETES SCI. & TECH. 23, 24 (2014). These numbers may undercount bias because biosimilars cannot be identical, unlike generics.

191. *Id.*

192. *Id.* at 25. Another stated that “you get what you pay for . . . .” *Id.*

193. See Emma Sullivan, James Piercy, John Waller, Christopher M. Black, & Sumesh Kachroo, *Assessing Gastroenterologist and Patient Acceptance of Biosimilars in Colitis and Crohn’s Disease Across Germany*, PLOS ONE, Apr. 2017, at 7.

194. See Ira Jacobs, Ena Singh, K. Lea Sewell, Ahmad AL-Sabbagh, & Lesley G. Shane, *Patient Attitudes and Understanding About Biosimilars: An Internal Cross-Sectional Survey*, 10 PATIENT PREFERENCE & ADHERENCE 937, 943–44 (2016).

195. Léa Frantzen, Jean-David Cohen, Sonia Tropé, Morgane Beck, Audrey Munos, Marie-Annick Sittler, Rita Diebolt, Isabelle Metzler, & Christelle Sordet, *Patients’ Information and Perspectives on Biosimilars in Rheumatology: A French Nation-Wide Survey*, 86 JOINT BONE SPINE 491, 495 (2019).

196. *Id.*

treat their rheumatic disease all admitted a negative opinion of biosimilars.<sup>197</sup>

The nocebo effect is also present with biosimilars.<sup>198</sup> There are a number of studies that report patient discontinuation after switching to a biosimilar based on purported lack of efficacy or vague side effects such as fatigue and headache without observable changes in disease state, consistent with the nocebo effect.<sup>199</sup> A systematic review found that the discontinuation rates were twice as high among patients who knew they were switched to a biosimilar versus double-blinded studies where patients did not know what treatment they were receiving.<sup>200</sup> This establishes a nocebo effect even though studies do not always use this term.<sup>201</sup> Patients switched

197. Marc Scherlinger, Emmanuel Langlois, Vincent Germain, & Thierry Schaevebeke, *Acceptance Rate and Sociological Factors Involved in the Switch from Originator to Biosimilar Etanercept*, 48 SEMINARS ARTHRITIS & RHEUMATISM 927, 929 (2019). In contrast, among patients willing to switch, only 11% had a negative view of generics. *Id.*

198. Not all agree that there is a documented nocebo effect. *E.g.*, Roy Fleischmann, Vipul Jairath, Eduardo Mysler, Dave Nicholls, & Paul Declerck, *Nonmedical Switching from Originators to Biosimilars: Does the Nocebo Effect Explain Treatment Failures and Adverse Events in Rheumatology and Gastroenterology?*, 7 RHEUMATOLOGY THERAPEUTICS 35, 37 (2020) (concluding that although there could be a nocebo effect, the studies to date are not rigorous enough to establish this conclusively). Admittedly, biologics are scientifically complicated, such that there could potentially be more differences for individual patients and some of the diseases treated by biologics may be measured by arguably subjective criteria such as joint pain. *See id.* at 40. Nonetheless, given that the nocebo effect has been well-documented to exist even with inert components, it seems logical that it would also exist with biologics.

199. *See* Avouac et al., *supra* note 181, at 747 (noting that more than 20% discontinued the biosimilar and the majority of these asserted inefficacy even though there was no independently verifiable issue); M. Chaparro, A. Garre, M.R. Guerra Veloz, J. M. Vazquez Moron, M.L. De Castro, E. Leo, E. Rodriguez, A. Y. Carbajo, S. Riestra, I Jimenez, X. Calvet, L. Bujanda, M. Rivero, F. Gommollon, J.M. Benitez, F. Bermejo, N. Alcaide, A. Guitierrez, M. Manosa, M. Iborra, R. Lorente, M. Rojas-Feria, M. Barreiro-de Acosta, L. Kolle, M. Va Domselaar, V. Amo, F. Arguelles, E. Ramirez, A. Morell, D. Bernardo, & J. P. Gisbert, *Effectiveness and Safety of the Switch from Remicade to CT-P13 in Patients with Inflammatory Bowel Disease*, 13 J. CROHN'S COLITIS 1380, 1384 (2019) (finding a higher rate of relapse among IBS patients switched to a biosimilar even though there were no noted medical differences between the groups, such that the researchers concluded the relapse was likely due to nocebo effect); E.M.H. Schmitz, P.J. Boekema, J.W.A. Straathof, D.C. van Renswouw, L. Brunsveld, V. Scharnhorst, M.E.C. van de Poll, M.A.C. Broeren, & L.J.J. Derijks, *Switching from Infliximab Innovator to Biosimilar in Patients with Inflammatory Bowel Disease*, 47 ALIMENTARY PHARMACOLOGY THERAPEUTICS 356, 359 (2017) (noting that one-quarter discontinued primarily due to subjective higher disease activity or adverse events); Lieke Tweehuysen, Bart J.F. Van den Bemt, Iris L. van Ingen, Alphons J.L. de Jong, Willemijn H. van der Laan, Frank H.J. van den Hoogen, & Alfons A. den Broeder, *Subjective Complaints as Main Reason for Biosimilar Discontinuation after Open Label Transitioning from Originator to Biosimilar Infliximab*, 70 ARTHRITIS RHEUMATOLOGY 60, 65–67 (2018) (finding no objective differences for those switched to an infliximab biosimilar, but some subjective differences such as reported tenderness); *see also* Mourad F. Rezek & Burkhard Pieper, *Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect*, 4 RHEUMATOLOGY THERAPY 209, 212 (2017) (suggesting multiple study results indicate a nocebo effect).

200. *See* Johlee S. Odinet, Chelsea E. Day, Jennifer L. Cruz, & Gregory A. Heindel, *The Biosimilar Nocebo Effect? A Systematic Review of Double-Blinded Versus Open-Label Studies*, 24 J. MANAGED CARE & SPECIALTY PHARMACY 952, 952 (2018) (finding that discontinuation for any reason was 14.3% for open-label studies versus 6.95% for double-blinded studies, and discontinuation for adverse effects was 5.6% in open-label studies versus 3.1% in double-blinded studies for multiple types of biosimilars).

201. *E.g.*, Christopher J. Edwards, Jana Hercogová, Helene Albrand, & Aurelian Amiot, *Switching to Biosimilars: Current Perspectives in Immune-Mediated Inflammatory Diseases*, 19 EXPERT OP. BIOLOGICAL THERAPY 1001, 1003 (2019); Anna La Noce & Marcin Ernst, *Switching from Reference*

back to original therapy “improved,” consistent with removal of the nocebo effect.<sup>202</sup> Along similar lines, new patients started on a biosimilar have similar discontinuation rates as those started on an originator biologic, suggesting that the nocebo effect explains the observational studies finding more discontinuation and alleged subjective problems with biosimilars.<sup>203</sup> Indeed, after reviewing the literature, a group of European clinicians from multiple fields concluded that the nocebo effect is underrecognized.<sup>204</sup>

The nocebo effect is particularly likely in switching cases (from originator biologic to biosimilar) as opposed to patients new to biologics. First, some patients may be opposed to switching based on a past negative experience with generics.<sup>205</sup> In addition, patients often desire to remain on a familiar medication, consistent with loss aversion, which requires the potential benefit of switching to be two times greater; this is impossible because a biosimilar should simply provide the same benefit as the corresponding originator biologic.<sup>206</sup> The nocebo effect is especially likely with biologics that treat serious conditions where it is common for patients to have tried several different previous treatments that did not work or had severe side effects.<sup>207</sup> In one survey, a substantial number of patients noted that if switched to a biosimilar, they would be more attentive to changes concerning safety and efficacy.<sup>208</sup> This increased attention might prompt a

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to *Biosimilar Products: An Overview of the European Approach and Real-World Experience So Far*, 3 EUR. MED. J., 74, 79 (2018) (discussing several studies yielding discontinuation and suggesting the nocebo effect may be at play); Mourad F. Rezk & Burkhard Pieper, *To See or NOsee: The Debate on the Nocebo Effect and Optimizing the Use of Biosimilars*, 35 ADVANCES THERAPY 749, 750–51 (2018) (discussing the various studies that have explored the phenomenon).

202. See Avouac et al., *supra* note 181, at 747; Fleischmann et al., *supra* note 198, at 56.

203. See Hans C. Ebbers & Huub Schellekens, *Are We Ready to Close the Discussion on the Interchangeability of Biosimilars?*, 24 DRUG DISCOVERY TODAY 1963, 1966 (2019).

204. See Pouillon et al., *supra* note 26, at 1181.

205. See Vincent Haghnejad, Catherine Le Berre, Yoann Dominique, Camille Zallot, Francis Guillemin, & Laurent Peyrin-Biroulet, *Impact of a Medical Interview on the Decision to Switch from Originator Infliximab to its Biosimilar in Patients with Inflammatory Bowel Disease*, 52 DIGESTIVE & LIVER DISEASE 281, 286–87 (2019) (finding patients who objected to switching reported lower overall satisfaction with past generics).

206. See Chiara Gasteiger, Maria Lobo, Nicola Dalbeth, & Keith J. Petrie, *Patients' Beliefs and Behaviours are Associated with Perceptions of Safety and Concerns in a Hypothetical Biosimilar Switch*, 41 RHEUMATOLOGY INT'L 163, 164 (2020) (a patient who has been using a brand medicine may be reluctant to switch as opposed to a patient who is new to a treatment); see also sources cited *supra* notes 135, 138 and accompanying text (discussing loss aversion).

207. E.g., GLOB. HEALTHY LIVING FOUND., PATIENT PERSPECTIVES ON MEDICATION SWITCHING FOR NON-MEDICAL REASONS 3 (2015), [https://www.50statenetwork.org/wp-content/uploads/2015/04/GHLF-Switching-Stable-Patients-Survey\\_Summary.pdf](https://www.50statenetwork.org/wp-content/uploads/2015/04/GHLF-Switching-Stable-Patients-Survey_Summary.pdf) (finding some patients are reluctant to try any new treatment for fear that their condition could worsen, even if existing treatment is not ideal); Yomei Shaw, Illinca D. Metes, Kaleb Michaud, Julie M. Donohue, Mark S. Roberts, Marc C. Levesque, & Judy C. Chang, *Rheumatoid Arthritis Patients' Motivations for Accepting or Resisting Disease-Modifying Antirheumatic Drug Treatment Regimens*, ARTHRITIS CARE & RSCH. June 2018, at 7–8.

208. See Frantzen, *supra* note 195, at 495 (providing results of French study surveying patients who suffer from rheumatoid arthritis).

nocebo effect.<sup>209</sup> Moreover, to the extent that a patient must switch to a biosimilar due to insurance coverage reasons, the nocebo effect is particularly likely to be triggered. Studies find patients indicate more adverse effects and allege diminished efficacy when switched to a biosimilar for cost as opposed to when they are switched for clinical reasons.<sup>210</sup>

### C. How Originator Biologics Benefit from the Biosimilars Bias

This Section evaluates the extent to which originator biologic manufacturers economically benefit from a bias against biosimilars, explaining their interest in perpetuating the bias. The U.S. biologics market is valued at \$211 billion<sup>211</sup> and constitutes 60% of global biologic sales.<sup>212</sup> Originator biologics account for most of these sales because only 19% of originator biologics face biosimilar competition in the United States.<sup>213</sup> Moreover, the market for biologics is rapidly expanding, increasing over 14% annually since 2014.<sup>214</sup>

The U.S. pharmaceutical market is of particular interest to originator biologic manufacturers because it is the largest.<sup>215</sup> Strong profits in the United States exist because, unlike other countries, the United States does not control prices and the federal government is barred from negotiating

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209. See *supra* notes 154–57 and accompanying text (discussing nocebo effect when patients believe they are taking the nonbrand drug); see also Fabrizio Cantini, Laura Niccoli, Giulia Franchi, Arianna Damiani, & Maurizio Benucci, *The Nocebo Effect in Rheumatology: An Unexplored Issue*, 22 *ISR. MED. ASS'N J.* 185, 188–89 (2020) (concluding that the nocebo effect could cause treatment failures in patients switched to biosimilars to treat inflammatory rheumatic diseases).

210. See Elaine Nguyen, Erin R. Weeda, Diana M. Sobieraj, Brahim K. Bookhart, Catherine Tak Piech, & Craig I. Coleman, *Impact of Non-Medical Switching on Clinical and Economic Outcomes, Resource Utilization and Medication-Taking Behavior: A Systematic Literature Review*, 32 *CURRENT MED. RSCH. & OP.* 1281, 1283 (2016) (finding almost 70% experienced negative outcomes); see also Douglas Wolf, Martha Skup, Hongbo Yang, Anna P. Fang, Andrew Kageleiry, Jingdong Chao, Manish Mittal, & Mark Lebwohl, *Clinical Outcomes Associated with Switching or Discontinuation from Anti-TNF Inhibitors for Nonmedical Reasons*, 39 *CLINICAL THERAPEUTICS* 849, 853 (2017) (finding that the majority of stable patients treated with anti-TNF who were switched for economic reasons had problems with disease control while the vast majority of those unswitched had well-controlled symptoms); Avouac et al., *supra* note 181, at 747 (finding that among patients at a French hospital switched to a biosimilar of infliximab, there were no differences in objective measurements, although some patients asserted differences, consistent with the nocebo effect); Richard H. Parrish II, *Biosimilar Interchangeability and Emerging Treatment Strategies for Inflammatory Bowel Diseases: A Commentary*, *GASTROENTEROLOGY INSIGHTS* 293, 296 (2021) (noting studies showing higher discontinuation rates for patients switched to biosimilars for nonmedical reasons).

211. See IQVIA, *supra* note 1, at 3.

212. DENIS KENT, SARAH RICKWOOD, & STEFANO DI BIASE, IQVIA, *DISRUPTION AND MATURITY: THE NEXT PHASE OF BIOLOGICS* 21 (2017).

213. See IQVIA, *supra* note 1, at 4, 9.

214. *Id.* at 3; see also Ying Chen, Alex Monnard, & Jorge Santos da Silva, *An Inflection Point for Biosimilars*, MCKINSEY & CO. (June 7, 2021), <https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilars> (noting that the global market is estimated to continue double-digit growth to double in size by 2025).

215. E.g., Matej Mikulic, *Distribution of the Total Global Pharmaceutical Market*, STATISTA (Mar. 9, 2021), <https://www.statista.com/statistics/266547/total-value-of-world-pharmaceutical-market-by-submarket-since-2006> (noting that the United States accounts for 48% of total global pharmaceutical sales).

lower prices for Medicare.<sup>216</sup> Recent proposed legislation to permit Medicare to engage in price negotiations for biologics has stalled.<sup>217</sup> It is not surprising that the biosimilar market is currently underdeveloped given that structural incentives in U.S. law do not promote the use of lower cost biosimilars. In addition, originator biologic manufacturers have entered into anticompetitive agreements with biosimilar manufacturers to prevent FDA-approved biosimilars from entering the market<sup>218</sup> and have entered contracts with insurance companies that mandate patients “fail first” on the originator biologic before biosimilar use can be authorized.<sup>219</sup>

The lucrative market in the United States works as a major incentive for companies to advance biases through marketing in the United States. As a result, U.S. doctors and consumers may be especially vulnerable to being exposed to marketing that exacerbates bias against biosimilars. The next Part explains how originator biologics capitalize on structural differences in the United States.

### III. FACTORS PERPETUATING BIAS AGAINST BIOSIMILARS

This Part turns to factors that perpetuate bias against biosimilars and explains why bias is more problematic for biosimilar uptake than for

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216. See 42 U.S.C. § 1395w-111(h)(i)(1) (barring government interference in negotiation between drug manufacturers and pharmacies on prices under Medicare Part D, which covers drugs dispensed from pharmacies); see also Rena M. Conti, Francis J. Crosson, Allan Coukell, & Richard G. Frank, *Reform Medicare Part B to Improve Affordability and Equity*, HEALTH AFFS. (June 25, 2021), <https://www.healthaffairs.org/doi/10.1377/hblog20210622.349716/full> (noting no price controls in the United States and recommending that Medicare be permitted to negotiate prices because negotiation estimated to save \$456 billion over a decade).

217. The House passed legislation that includes Medicare price negotiation for biologics. See Build Back Better Act, H.R. 5376, 117th Cong. § 139001I (2021) (as passed by the U.S. House of Representatives on Nov. 19, 2021); Juliette Cubanski, Tricia Neumann, & Meredith Freed, *Explaining the Prescription Drug Provisions in the Build Back Better Act*, KAISER FAM. FOUND. (Nov. 23, 2021), <https://www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-build-back-better-act> (noting that the pending legislation would create an exception to current law regarding Medicare Part D that would permit the government to negotiate prices for a small number of the most expensive drugs starting in 2025 and for Part B starting in 2027). Some have criticized this provision as permitting not price negotiation, but mandatory price reduction. See Jonathan Weisman & Emily Cochrane, *Democrats Add Drug Cost Curbs to Social Policy Plan, Pushing for Vote*, N.Y. TIMES (Nov. 6, 2021), <https://www.nytimes.com/2021/11/02/us/politics/prescription-drug-prices-medicare.html>; see also Elizabeth Bauer, *The Prescription Drug Price Negotiation Plan in the Biden BBB Bill Is Not What It's Claimed to Be*, FORBES (Nov. 6, 2021, 6:18 PM), <https://www.forbes.com/sites/ebauer/2021/11/06/the-prescription-drug-price-negotiation-plan-in-the-biden-bbb-bill-is-not-what-its-claimed-to-be>. However, the biggest issue is whether this bill will pass. Alexander Bolton, *Biden's Build Back Better Suddenly In Serious Danger*, THE HILL (Dec. 16, 2021, 1:34 PM), <https://thehill.com/homenews/senate/586147-bidens-build-back-better-bill-suddenly-in-serious-danger>.

218. Eric Grannon & Adam M. Acosta, *FTC and FDA Announce Plans to Combat Anticompetitive Practices in the “Biologic Marketplace,”* WHITE & CASE (Feb. 12, 2020), <https://www.white-case.com/publications/alert/ftc-and-fda-announce-plans-combat-anticompetitive-practices-biologic-marketplace>.

219. See Van de Wiele et al., *supra* note 6, at 1202 (noting settlements from litigation); see also Tony Hagen, *Pfizer Resolves Antitrust Lawsuit with J&J Over Remicade*, CTR. FOR BIOSIMILARS (July 22, 2021), <https://www.centerforbiosimilars.com/view/pfizer-resolves-antitrust-lawsuit-with-j-j-over-remicade>; Stanton Mehr, *Contracting ‘Schemes’ to Prevent Biosimilar Infliximab Access: Let’s Drop the Feigned Outrage*, BIOSIMILARS REV. & REP. (July 18, 2018), <https://biosimilarsrr.com/2018/07/18/contracting-prevent-biosimilar-infliximab-access>.

generic uptake given legal and structural differences. This Part begins by explaining the contribution of U.S. regulatory laws and policies to bias and then turns to direct actions by companies,<sup>220</sup> in conjunction with patient groups, that improperly emphasize differences and perpetuates bias. Finally, this Part highlights current financial disincentives against biosimilars as well as how cognitive biases exacerbate mismarketing efforts to sustain an unnecessary bias against biosimilars.

#### A. U.S. Law

There are several aspects of U.S. law that may promote unnecessary bias against biosimilars. As discussed earlier, the United States is the only country that: (1) requires an additional regulatory designation of interchangeability to permit pharmacy substitution of biologics and (2) requires that a biosimilar have a different nonproprietary name than its related originator biologic.<sup>221</sup> These differences make it challenging to substitute a biosimilar for an originator biologic, challenges not faced by generics. The differences can also be improperly utilized to promote the perception that biosimilars are inferior.

##### 1. Interchangeability Designation and State Laws

The existence of an interchangeability designation inherently promotes a bias against biosimilars not designated as interchangeable. Because generics do not need such a designation to be substituted, doctors and patients may mistakenly believe that only interchangeable biosimilars can be safely used—as highlighted in the discussion about doctor and patient bias against biosimilars.<sup>222</sup> A separate interchangeable designation was proposed in initial U.S. legislation concerning a biosimilar pathway and likely reflects scientific differences between biologic and traditional drugs.<sup>223</sup> The designation was in part due to hesitancy concerning whether biosimilars should be substituted without doctor intervention.<sup>224</sup>

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220. This Part treats patients and doctors as broad groupings although there are of course differences within each of these groups. See Sarnola et al., *supra* note 178, at 17 (noting that men and those more familiar with brand name drugs were less likely to use biosimilars).

221. See *supra* note 66 and accompanying text (U.S. interchangeability designation is unique); Zachary Brennan, *Canada Steers Away From Using Suffixes in Biologics' Names*, REGUL. AFFS. PROS. SOC'Y (Feb. 18, 2019) <https://www.raps.org/news-and-articles/news-articles/2019/2/canada-steers-away-from-using-suffixes-in-biosimil> (noting U.S. naming convention is unique in the world); see also Brad Jordan, *U.S. Biologics and Biosimilars Need Distinguishable Names*, STAT (Apr. 23, 2019), <https://www.statnews.com/2019/04/23/biologics-biosimilars-distinguishable-names> (comparing U.S. approach to other countries' approaches as well as justification for different views).

222. See discussion *supra* Sections II.A–B (discussing the bias against biosimilars).

223. See Krista Hessler Carver, Jeffrey Elikan, & Erika Lietzan, *An Unofficial Legislative History of Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L. J. 671, 700–01, 720 (2010) (discussing legislative history of interchangeability bills and noting the Center for Drug Evaluation & Research's 2003 concern questioning absolute therapeutic interchangeability between originator drugs and their subsequent biologics).

224. *Id.* at 733–34 (noting that there were competing views concerning whether interchangeability was appropriate including that the EU had noted that biosimilars were different than generics). Even in 2017 when the FDA considered standards for how to demonstrate interchangeability, some

However, today, global practice indicates no need to be cautious in using biosimilars not labeled as interchangeable. There have been over 14,000 successful switches from an originator biologic to a biosimilar without this designation,<sup>225</sup> in addition to a plethora of rigorous double-blinded studies showing no problems with switching patients to biosimilars.<sup>226</sup> Based on strong indications of biosimilar safety, Australia relaxed the considerations required to recommend substitution of a biosimilar.<sup>227</sup> Also, beyond laws to promote automatic substitution, based on current science, some have suggested that all EU-approved biosimilars should be considered clinically interchangeable after a decade of unproblematic use.<sup>228</sup> Even in the United States, some have suggested that at least for insulin, the interchangeability standard should be waived because typical concerns with biologics, such as immunogenicity, have not been an issue.<sup>229</sup>

In contrast to the global trend towards promoting biosimilar use and despite the interchangeable designation that allows for biosimilar substitution, U.S. state laws make substitution more difficult—dissimilar to state laws that promote generic use.<sup>230</sup> Most states have laws limiting substitution to only biosimilars deemed interchangeable, which requires substantially more clinical data beyond that required for a biosimilar not classified as interchangeable.<sup>231</sup> These laws make substitution less likely by requiring notice to doctors and patients and by sometimes permitting objection to substitution.<sup>232</sup> Beyond notification requirements, some state laws impose burdensome record keeping requirements that may further disincentivize substitution of a biosimilar.<sup>233</sup> Notably, these requirements were

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physicians remained concerned about interchangeability. See Jackie Syrop, *Physicians Express Concerns About Biosimilar Interchangeability to FDA*, AM. J. MANGAGED CARE (June 30, 2017), <https://www.centerforbiosimilars.com/view/physicians-express-concerns-about-biosimilar-interchangeability-to-fda>; see also GaBI J. Ed., *Physician Associations Comment on FDA's Interchangeability Guidance*, 6 GENERICS & BIOSIMILARS INITIATIVE J., June 2017, at 120–21 (summarizing physician comments to FDA concerning interchangeability guidance).

225. BIOSIMILARS FORUM, *supra* note 81, at 8.

226. See *supra* note 181 and accompanying text.

227. See AUSTL. GOV'T DEP'T OF HEALTH, PUBLIC SUMMARY DOCUMENT—MARCH 2018 PBAC MEETING, Mar. 2018, at 3 (noting no safety issues in EU since first biosimilar registration in 2006 as well as published studies showing no issues with switching patients to biosimilar).

228. See Kurki, *supra* note 66, at 84; MEDICINES FOR EUROPE, POSITIONING STATEMENTS ON PHYSICIAN-LED SWITCHING FOR BIOSIMILAR MEDICINES, Sept. 2020, at 4; Ebberts & Schellekens, *supra* note 203, at 1963.

229. Mariana P. Socal & Jeremy A. Greene, *Interchangeable Insulins — New Pathways for Safe, Effective, Affordable Diabetes Therapy*, 382 NEW ENG. J. MED. 981, 981–82 (2020).

230. E.g., Aaron Hakim & Joseph S. Ross, *Obstacles to the Adoption of Biosimilars for Chronic Diseases*, 317 J. AM. MED. ASS'N 2163–64 (2017); Katherine Macfarlane, *Camouflaging State Biosimilar Laws as Pro-Patient Legislation*, 26 ANNALS HEALTH L. 52, 58–59 (2017).

231. See Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, NAT'L CONF. OF STATE LEG. (May 3, 2019), <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>.

232. *Id.*

233. See *id.* The first state-level biosimilar legislation making substitution complicated was opposed by pharmacists concerned about “too much red tape for substitution.” See Macfarlane, *supra*

generally imposed not because of scientific concerns, but because of extensive lobbying by self-interested brand companies.<sup>234</sup>

## 2. Nonproprietary Naming

The United States has a distinct naming regulation for biosimilars that may further suggest to doctors and patients that biosimilars are different and suspect. Unlike generic drugs, which share the exact nonproprietary (i.e., not trademarked) name as the related brand drug, biosimilars do not share an identical nonproprietary name with the originator biologic. For example, the brand drug Nexium, commonly used to treat heartburn, has the identical nonproprietary name, esomeprazole, as all generic versions of the drug.<sup>235</sup> In contrast, the United States requires that biosimilars use a four-letter random suffix unrelated to the manufacturer name.<sup>236</sup> For example, the originator biologic Remicade has the nonproprietary name “infliximab,” whereas biosimilars include “infliximab-dyyb” and “infliximab-abda.”<sup>237</sup>

Different names for biosimilars and their corollary originator biologics suggests caution and skepticism concerning biosimilars. Indeed, the FTC previously cautioned this could result in unnecessary costs by improperly signaling a false distinction to doctors and patients.<sup>238</sup> Moreover, given that there remains some bias against generics despite identical nonproprietary names, those with an existing bias against generics are especially likely to be biased against biosimilars named differently than originator biologics.<sup>239</sup>

The FDA’s rationale for using distinct names does not align with promoting biosimilar use. The FDA has stated that different names were needed to track adverse events, prevent inadvertent substitution by

note 230, at 66; see also Norman V. Carroll, Jack E. Fincham, & Fred M. Cox, *The Effects of Differences in State Drug Product Selection Laws on Pharmacists’ Substitution Behavior*, 25 MED. CARE 1069, 1069 (1987) (finding more substitution in states that did not require additional record keeping and did not require patient consent).

234. See Macfarlane, *supra* note 230, at 66–67.

235. *Generic Nexium Availability*, DRUGS.COM, (Jan. 12, 2022), <https://www.drugs.com/availability/generic-nexium.html>.

236. HHS, FDA, CDER, & CBER, NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY 5–6 (2019) (draft guidance document) [hereinafter 2019 DRAFT NAMING GUIDANCE]. In the 2019 draft guidance document, the agencies reversed their prior guidance that originator biologics should be given suffixes retroactively upon approval. *Id.* at 5.

237. *Infliximab (Rx)*, MEDSCAPE, <https://reference.medscape.com/drug/remicade-inflextra-infliximab-343202> (last visited Mar. 21, 2022); see also Nancy J. Globus, *Alphabet Soup: The Story Behind Biosimilar Name Suffixes*, AM. J. MANAGED CARE (Aug. 8, 2020), <https://www.centerforbiosimilars.com/view/alphabet-soup-the-story-behind-biosimilar-nonproprietary-name-suffixes> (explaining naming for biosimilars).

238. Fed. Trade Comm’n, Comment on HHS and FDA’s Guidance for Industry on the “Nonproprietary Naming of Biologic Products; Draft Guidance for Industry; Availability,” at 2–3 (Oct. 27, 2015); see also *Suffix v. Non Suffix: Naming Biosimilars*, AAM: BIOSIMILARS COUNCIL (Oct. 21, 2019), <https://biosimilarscouncil.org/resource/naming-biosimilars-suffix> (stating that different naming may improperly suggest biosimilars are not as safe and effective as originators and thus, negatively impact biosimilar use).

239. See discussion *supra* Section I.C; Gasteiger et al., *supra* note 206, at 163 (noting that biosimilar naming affects patients’ perceptions of whether biosimilars are appropriate).



pharmacists, and ensure doctors do not inadvertently assume biosimilars are interchangeable.<sup>240</sup> However, adverse event tracking does not require distinct nonproprietary names; in reality, virtually all adverse event reports involving biologics use brand names.<sup>241</sup> Indeed, Europe has a much longer and more extensive use of biosimilars with identical nonproprietary names and uses brand names for all biologics, including biosimilars, without negative health outcomes.<sup>242</sup> In addition, pharmacists are unlikely to make inadvertent substitutions given that they already rely on the FDA-published *Orange Book* to see if a generic can be safely substituted, and there is no basis for assuming they would make improper assumptions for biologics.<sup>243</sup>

## B. Beyond Regulatory Issues

### 1. Advertising and Promotion Exacerbate Bias Against Biosimilars

This Section explores how marketing and social media campaigns capitalize on U.S. regulatory oddities and other issues to establish and perpetuate bias against biosimilars. This Section focuses on three issues that perpetuate bias against biosimilars by activating the availability bias that all individuals are susceptible to. The first misleading issue is that biosimilars are not scientifically identical. The second misleading issue involves aspects of U.S. law where biosimilars are treated differently than generics. The third misleading issue concerns overhyped dangers of switching to a biosimilar. The power of these messages has been underscored by similar messages from patient advocate groups,<sup>244</sup> many of which are funded by pharmaceutical companies.<sup>245</sup>

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240. HHS, FDA, CDER & CBER, NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR THE INDUSTRY 4–5 (2017) [hereinafter 2017 DRAFT NAMING GUIDANCE].

241. Fed. Trade Comm'n, *supra* note 238, at 13.

242. EMA & EUR. COMM'N, *supra* note 67, at 24–26; *see also* AUSTL. GOV'T DEP'T OF HEALTH, *supra* note 227227, at 2–3 (noting Australia's use of the same name without suffix).

243. Fed. Trade Comm'n, *supra* note 238, at 14. Moreover, a different name for interchangeable biosimilars could prevent pharmacists from substituting it for the equivalent biologic due to state laws that require the identical name for automatic substitution. *Id.* at 14 n.52.

244. Patient groups have a history of advancing pharmaceutical industry interests. *See* Emily Kopp & Rachel Bluth, *Nonprofit Linked to PhRMA Rolls Out Campaign to Block Drug Imports*, KAISER HEALTH NEWS (Apr. 19, 2017), <https://khn.org/news/non-profit-linked-to-phrma-rolls-out-campaign-to-block-drug-imports> (noting a patient group's opposition to drug importation legislation in sync with pharmaceutical lobbying group PhRMA); *see also* Susannah L. Rose, *Patient Advocacy Organizations: Institutional Conflicts of Interest, Trust and Trustworthiness*, 41 J. L. MED. & ETHICS 680, 682 (2013) (noting a nonprofit group for mental health promoted use of antidepressants and downplayed risk of suicide consistent with industry). At the extreme, a drug company succeeded in using a seemingly grassroots campaign to promote a drug previously rejected to treat low desire in women that had been deemed dangerous. Ray Moynihan, *Commentary: The Voice of the People, Funded Now by Your Friendly Pharmaceutical Company*, 17 BIOETHICAL INQ. 61, 61 (2020).

245. *E.g.*, Alice Fabbri, Lisa Parker, Paola Mosconi, Giussy Barbara, Maria Pina Frattaruolo, Edith Lau, Cynthia M. Kroeger, Carole Lunny, Douglas M. Salzwedel, & Barbara Mintzes, *Industry Funding of Patient and Health Consumer Organisations: Systematic Review with Meta-Analysis*, 368 BRIT. MED. J., Dec. 2020, at 9, 11 (finding industry funding of patient advocacy groups is common, yet fewer than 30% of these groups typically disclose this funding on their websites); Rose, *supra* note 244, at 681 (noting conflict of interest problems); Emily Kopp, Sydney Lupkin, & Elizabeth Lucas,

### a. Capitalizing on the Nonidentical Nature of Biosimilars

Manufacturers of originator biologics repeatedly highlight scientific differences when promoting a bias against biosimilars. For example, Genentech's website states that the FDA requires a biosimilar to be "very similar to the original medicine, but not identical [to the reference product]."<sup>246</sup> Additionally, there is substantial discussion of how biosimilars are not generics, which can play upon the existing bias against generics.<sup>247</sup> For example, an article posted on Genentech's website highlights a quote in large font: "[E]ven with the most advanced technologies, scientists can't make exact copies of biologics. That's why they're called biosimilars."<sup>248</sup>

These statements are correct, yet misleading. It is of course true that biosimilars are not identical copies.<sup>249</sup> However, the FDA and other agencies approve these highly similar, albeit not identical, drugs because they are considered just as safe and effective as their comparable biologics.<sup>250</sup> What marketing suggests is a flaw is in fact the intended goal of the system. As explained earlier, even different batches of biologics from the originator company are not identical such that focusing on identity is inappropriate. Moreover, some doctors, scientists, and policymakers outside the United States do consider biosimilars to be medically interchangeable with the originator biologics.<sup>251</sup> Nonetheless, these misleading statements are likely believed by patients who have an existing bias against generics, leading them to be especially suspicious of biosimilars that are not identical, unlike generics.<sup>252</sup> Even for those without an existing bias against generics, hearing these distorted truths frequently repeated by drug companies and patient advocacy groups establishes an availability bias.<sup>253</sup>

### b. Capitalizing on Legal Distinctions of Interchangeability and Different Names

A related issue is a repeated yet misleading suggestion that a biosimilar is unsafe if it is not interchangeable. For example, Janssen, maker of originator biologic Remicade, issued a brochure in 2017, two years before the FDA set requirements for what would be interchangeable, that

*Patient Advocacy Groups Take in Millions from Drug Makers. Is there a payback?*, KAISER HEALTH NEWS (Apr. 6, 2018), <https://khn.org/news/patient-advocacy-groups-take-in-millions-from-drugmakers-is-there-a-payback> (noting that in 2015, donations to these groups were slight compared to the amount that companies spent on federal lobbying).

246. *Understanding Biosimilars*, GENENTECH (June 1, 2017), <https://www.gene.com/stories/understanding-biosimilars>.

247. See discussion *supra* Section I.C.

248. Myriam Mendila, *Similar, Not the Same: The Road Ahead for Biosimilars*, GENENTECH (June 2, 2016), <https://www.gene.com/stories/similar-not-the-same-the-road-ahead-for-biosimilars>.

249. See, e.g., sources cited *supra* note 55.

250. See, e.g., sources cited *supra* note 38–39.

251. E.g., Ebbers & Schellekens, *supra* note 203, at 1963–64; Afzali et al., *supra* note 66, at 2080–81 tbl.2.

252. See discussion *supra* Section I.C.2.

253. See discussion *supra* Section III.B.1.

emphasized that no biosimilar has met the requirements for interchangeability.<sup>254</sup> The current Remicade website still states that no Remicade biosimilar is interchangeable.<sup>255</sup> Although legally true, it improperly suggests a problem with biosimilars to Remicade.<sup>256</sup> This is especially disingenuous because all biosimilars to Remicade are administered by infusion<sup>257</sup> such that it could not be dispensed at a pharmacy—the only setting where interchangeability is relevant.<sup>258</sup> Discussion of interchangeability to Remicade is a red herring.

Another misleading marketing document suggests that only interchangeable biosimilars are safe with the heading “high standards should be non-negotiable” before the discussion of interchangeability.<sup>259</sup> This section is misleading as it states, “substitution of a biosimilar in place of an original biologic medicine should only occur if the biosimilar is deemed interchangeable by the FDA,”<sup>260</sup> which suggests that interchangeability is always an issue. However, only a minority of current biosimilars could be interchangeable because the majority are not sold in pharmacies.<sup>261</sup> Interestingly, companies do not mention that scientific studies to date have found no problems resulting from the same type of multiple switching between a biosimilar and its biologic that would be used to seek interchangeable status for such biosimilars.<sup>262</sup>

Statements by associations may also suggest that interchangeability is important based on statements made by individuals that are associated with originator biologics. For example, when the FDA approved the first biosimilar to Remicade, the Spondylitis Association for America, which advocates for patients,<sup>263</sup> issued a statement that included a quote from Johnson & Johnson that the newly approved biosimilar, Inflectra, was not

254. See Pfizer, Citizen Petition to Request that the FDA Issue Guidance to Ensure Truthful and Non-Misleading Communications by Sponsors Concerning the Safety and Effectiveness of Biosimilars, Including Interchangeable Biologics, Relative to Reference Product(s), at 8 (Aug. 22, 2018), <https://www.regulations.gov/document/FDA-2018-P-3281-0001> (noting that biosimilar Inflectra is not interchangeable, and no biosimilar to Remicade has established interchangeability).

255. *Biosimilars FAQ*, REMICADE, <https://www.remicade.com/additional-resources.html#biosimilar> (last visited Feb. 6, 2022).

256. Pfizer, *supra* note 254, at 8.

257. E.g., *Infliximab*, CROHN'S & COLITIS UK, at 8 (2021), [http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Infliximab\\_Ed\\_8b\\_Nov\\_2021\\_.pdf](http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Infliximab_Ed_8b_Nov_2021_.pdf) (explaining that all versions of infliximab are administered by infusion or injection).

258. See *supra* notes 59–60 and accompanying text (explaining that interchangeability only applies to biosimilars dispensed by pharmacies).

259. Mendila, *supra* note 248.

260. *Id.*

261. See discussion *supra* Section I.A.2.

262. See A. Blauvelt, J.-P. Lacour, J.F. Fowler Jr., J.M. Weinberg, D. Gospodinov, E. Schuck, J. Jauch-Lembach, A. Balfour, & C.L. Leonardi, *Phase III Randomized Study of the Proposed Adalimumab Biosimilar GP2017 in Psoriasis: Impact of Multiple Switches*, 179 BRIT. J. DERMATOLOGY 623, 623 (2018); see also Hiroaki Matsuno & Tsukasa Matsubara, *A Randomized Double-Blind Parallel-Group Phase III Study to Compare the Efficacy and Safety of NI-071 and Infliximab Reference Product in Japanese Patients with Active Rheumatoid Arthritis Refractory to Methotrexate*, 29 MODERN RHEUMATOLOGY 919, 924 (2018).

263. *Our Mission & Vision*, SPONDYLITIS ASS'N OF AMERICA, <https://spondylitis.org/about-saa/our-mission-vision> (last visited Mar. 21, 2022).

approved as interchangeable.<sup>264</sup> The press release also quoted a doctor stating that the approval does not have any language or data “that would allow forced change from Remicade use.” However, the FDA only has authority to approve drugs and cannot force patients to change drugs.

There is some evidence that doctors are responding to this marketing. A 2020 study found that the vast majority (86%) of U.S. rheumatologists already prescribing biologics thought that it was very important for a label to indicate whether a biosimilar is interchangeable despite the designation only applying to biosimilars dispensed at a pharmacy.<sup>265</sup> Notably, unlike some prior studies, most of these doctors (83%) asserted that they were very or extremely familiar with the fact that biosimilars have no clinically meaningful differences.<sup>266</sup> Although the study suggested that doctors may not truly understand the biosimilar definition they allege to be familiar with, an alternative theory is that they are influenced by marketing. Importantly, the doctors surveyed prescribed a type of biologic not available to patients for purchase at a pharmacy, making the interchangeability designation irrelevant.<sup>267</sup> Marketing that suggests that interchangeability is important, even for biologics that are not available at a pharmacy, could be misleading these doctors.

Companies have also suggested that different nonproprietary names between an originator and biosimilar suggest key differences, reinforcing biosimilar bias. A 2018 tweet by Amgen stated, “While #biosimilars may be highly similar to their #biologic reference products, there’s still a chance that patients may react differently. *See what you’re missing without the suffix[.]*”<sup>268</sup> Technically, even with generic drugs that, by definition, have identical active ingredients, patients may react differently because of inactive ingredients, the approved range of bioequivalence, or both.<sup>269</sup> Nonetheless, a patient seeing the tweet could easily assume that a lack of a suffix or a different suffix is very important.<sup>270</sup> Indeed, one study

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264. *FDA Approves the First Biosimilar Medication for Ankylosing Spondylitis and Psoriatic Arthritis*, SPONDYLITIS ASS’N OF AM., <https://spondylitis.org/research-new/fda-approves-the-first-biosimilar-medication-for-ankylosing-spondylitis-and-psoriatic-arthritis> (last visited Mar. 21, 2022).

265. Allan Gibofsky & Dorothy McCabe, *US Rheumatologists’ Beliefs and Knowledge about Biosimilars: A Survey*, 60 RHEUMATOLOGY 896, 898 (2020) (“86% [of study respondents] felt it important/very important for interchangeable approval to be on the label.”).

266. *Id.* About three-quarters of these doctors considered effectiveness to be either the most important or second most important factor in considering whether to use a biosimilar, although this seemed only a consideration for patients starting biologic treatment, as opposed to those already doing well on the reference product. *Id.* at 898–900.

267. *Id.* at 896 (noting surveyed doctors prescribed TNF inhibitors).

268. See Ned Pagliarulo, *Pfizer Calls Out Pharma Peers for ‘Scare Tactics’ on Biosimilars*, BIOPHARMADIVE (Aug. 29, 2018) (emphasis added) (reporting on the April 13, 2018 tweet).

269. See Jacinthe Leclerc, Claudia Blais, Louis Rochette, Denis Hamel, Line Guénette, & Paul Poirier, *Impact of the Commercialization of Three Generic Angiotensin II Receptor Blockers on Adverse Events in Quebec, Canada: A Population-Based Time Series Analysis*, 10 CIRCULATION: CARDIOVASCULAR QUALITY & OUTCOMES, Oct. 2017, at 7.

270. See Association for Accessible Medicines, Comments of the Association for Accessible Medicines and the Biosimilars Council on Behalf of Our Member Companies: Nonproprietary Naming of Biological Products, at 4 (May 7, 2019) (noting FDA’s concern that suffixes could be misinterpreted

indicates individuals shown a print advertisement for a fictitious biosimilar with a nonproprietary name that included a suffix were less likely to use the biosimilar compared to the originator with no suffix.<sup>271</sup> Although study participants were told that the biosimilar had no meaningful differences in terms of efficacy, safety, and purity, the suffix distinction nonetheless created bias.<sup>272</sup>

### c. Overhyping Dangers of Switching to Biosimilars

In addition to the foregoing issues, companies have made statements to discourage switching from the originator biologic to its biosimilar by framing it as risky despite the robust regulatory approval process that contemplates such a switch. For example, an alliance of companies warned biosimilars could “put you in the emergency room” even though biosimilars are only approved if they have no clinically meaningful differences from the originator biologics.<sup>273</sup> Even worse, the chairman of Biotechnology Innovation Organization’s (BIO) international advisory board suggested that moving patients to biosimilars should be approached cautiously “so we don’t end up with another thalidomide.”<sup>274</sup> Referencing a drug that caused many birth defects in the 1960s conjures serious concern, yet is inapplicable. After all, modern drug regulation developed as a result of this tragedy, and the United States never approved thalidomide at the time it was causing birth defects.<sup>275</sup>

These statements vastly overstate potential problems and promote an unnecessary bias against biosimilars. In Europe, where biosimilars have been marketed since 2006, patients in multiple drug classes who have switched to a biosimilar from an originator biologic have not encountered safety or efficacy problems.<sup>276</sup> Similarly, scientific studies have found no problems with switching to biosimilars such as infliximab, adalimumab, etanercept, and rituximab.<sup>277</sup> Some countries have been adequately

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as indicating that biosimilars are clinically different or inferior); FTC, Statement of the Federal Trade Commission to the Department of Health and Human Services Regarding the HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, at 16 (July 16, 2018).

271. See Mariana P. Socal, Jace B. Garrett, William B. Tayler, Ge Bai, & Gerard F. Anderson, *Naming Convention, Interchangeability and Patient Interest in Biosimilars*, 33 *DIABETES SPECTRUM* 273, 273, 275 (2020). *But see* Kolbe et al., *supra* note 166, at 369 (asserting that biosimilar names did not impact willingness to prescribe drugs, although this study relied on self-reporting).

272. Socal et al., *supra* note 271, at 273, 275.

273. E.g., Christopher Rowland, *Marketers Are Having a Field Day: Patients Stuck in Corporate Fight against Generic Drugs*, *WASH. POST* (Jan. 9, 2019), [https://www.washingtonpost.com/business/economy/drugmakers-alleged-scare-tactics-may-hold-back-competition/2019/01/09/612ac994-046d-11e9-9122-82e98f91ee6f\\_story.html](https://www.washingtonpost.com/business/economy/drugmakers-alleged-scare-tactics-may-hold-back-competition/2019/01/09/612ac994-046d-11e9-9122-82e98f91ee6f_story.html); *see also* Pfizer, *supra* note 254, at 7–9.

274. Rowland, *supra* note 273.

275. See Bara Fintel, Athena T. Samaras, & Edson Carias, *The Thalidomide Tragedy: Lessons for Drug Safety and Regulation*, *HELIX* (July 28, 2009) <https://www.helix.northwestern.edu/2009/07/28/the-thalidomide-tragedy-lessons-for-drug-safety-and-regulation>.

276. See *EUR. MEDS. AGENCY & EUR. COMM’N*, *supra* note 66, at 24.

277. See Hillel P. Cohen, Andrew Blauvelt, Robert M. Rifkin, Silvio Danese, Sameer B. Gokhale, & Gillian Woollett, *Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes*, 78 *DRUGS* 463–476 (2018) (summarizing review of various studies

persuaded by the existing evidence and now mandate that patients use biosimilars<sup>278</sup> or at least strongly encourage switching through incentives.<sup>279</sup>

A related issue is that companies and patient groups have argued against so-called “non-medical switching”<sup>280</sup> to biosimilars when insurance coverage requires stable patients on an originator biologic to switch to its biosimilar.<sup>281</sup> For example, the Patient Access Collaborative has videos and fact sheets suggesting a problem with titles such as “non-medical switching hurts patients.”<sup>282</sup> Similarly, the National Infusion Center Association states that “[n]on-medical switching is a strategy that health insurers use to control their costs by forcing stable patients to switch . . . to drugs that may not be as effective.”<sup>283</sup> It asserts, without citation, that “when a patient switches off a medication and later switches back onto the same medication after failing other medication(s), that once effective treatment may lose its effectiveness . . . .”<sup>284</sup>

These arguments might be persuasive to those that are already skeptical of biosimilars but are inconsistent with other facts. For example, in countries where the payor is the government, the government would have no interest in an action that results in higher costs—assuming that governments are engaging in logical cost-saving action, they would prefer the equally-effective, lower-cost biosimilar. In addition, over time, more governments that pay for drugs are strongly recommending, or even requiring,

concerning infliximab, epoetin, filgrastim, etanercept, and adalimumab that found great majority of studies surveyed concluded no differences in efficacy or immunogenicity compared to remaining on an existing reference biologic, including three large multiple switch studies showing no problems after multiple switches); see also Inotai, *supra* note 181, at 915; Edwards et al., *supra* note 201, at 1004.

278. E.g., Kelly Davio, *Regulator Explains How Denmark Has Achieved Its Biosimilar Success*, CTR. FOR BIOSIMILARS (Mar. 21, 2019), <https://www.centerforbiosimilars.com/view/regulator-explains-how-denmark-has-achieved-its-biosimilar-success> (noting that Denmark requires that patients use biosimilars); Skylar Jeremias, *Rising Costs Explain Why Canada is Switching to Biosimilars*, CTR. FOR BIOSIMILARS (June 15, 2020), <https://www.centerforbiosimilars.com/view/rising-costs-explain-why-canada-is-switching-to-biosimilars> (noting Canadian provinces that require biosimilar use).

279. E.g., INESSS, *supra* note 69, at 36.

280. Although “non-medical switching” has been used broadly to refer to any coverage-based switch to a biosimilar, some have suggested that this term is overbroad and imprecise. See Kayt Sukel, *The Fight to End Misleading Info on Biosimilars*, MANAGED HEALTHCARE EXEC. (April 1, 2019), <https://www.managedhealthcareexecutive.com/view/fight-end-misleading-info-biosimilars> (“[T]erms . . . like ‘non-medical switching’ are deliberately misleading—and may scare providers and patients away from using equally effective but less expensive treatment drugs.”).

281. See *Non-Medical Switching*, PATIENT ACCESS COLLABORATIVE, <https://www.patientaccesscollaborative.org/nms> (last visited Mar. 21, 2022); Patient Access Collaborative, *Barriers to Patient Access: Non-Medical Switching*, YOUTUBE (June 15, 2020), [https://youtu.be/Hrh3Ma\\_u5Uo](https://youtu.be/Hrh3Ma_u5Uo); *How Non-Medical Switching Hurts Patients*, ALLIANCE FOR PATIENT ACCESS, <https://admin.allianceforpatientaccess.org/wp-content/uploads/2020/01/AfPA-How-NMS-Hurts-Patients.pdf> (“A national study shows that [non-medical switching] can hurt nearly every aspect of patients’ lives . . . .”); Alliance for Patient Access, *Non-Medical Switching Hurts Patients*, FACEBOOK (Jan. 8, 2020), <https://www.facebook.com/patientaccess/videos/non-medical-switching-hurts-patients/463081841310061> (asserting that among those who switched, many needed additional care including hospitalization); *What is Non-Medical Switching*, NAT’L INFUSION CTR. ASS’N (“NICA”), <https://infusion-center.org/education/non-medical-switching> (last visited Mar. 21, 2022) [hereinafter NICA].

282. See sources cited *supra* note 283.

283. NICA, *supra* note 283.

284. *Id.*

patients to switch to biosimilars to expand patient coverage, reflecting an understanding that switching is safe and cost-effective.<sup>285</sup>

Nonetheless, advocacy against non-medical switching may be effective for some doctors and patients. In one survey of EU physicians, 60% were comfortable switching stable patients to biosimilars, but when the same physicians were asked the same question using the term “non-medical switching,” only 42% were comfortable.<sup>286</sup> A study of U.S. patients found that the vast majority tried to avoid switching and were willing to pay more to avoid the switch; almost 20% were willing to pay \$200 or more per visit, which would result in additional out-of-pocket costs of more than \$2,000 in many cases.<sup>287</sup> In addition, over 40% of switched patients claimed they experienced more side effects with the new biologic<sup>288</sup> consistent with prior observational (not blinded) studies where patients had negative outcomes after they knew they were switched to a biosimilar due to payor request.<sup>289</sup> These results are consistent with a nocebo effect caused by the highly available statements by companies and patient advocates alike against switching, which prompts the cognitive bias of loss aversion that makes patients highly averse to change.

## 2. Financial Disincentives

Bias against biosimilars is influenced by payor preferences, as well as laws governing Medicare reimbursement that typically disincentivize biosimilar use. Although originator biologic companies have a role in skewing financial disincentives with rebates to pharmacy benefit managers (who negotiate drug benefits for insurance companies) to promote use of originator biologics, this Section will first focus on Medicare given that it often has a major influence on private insurers and doctors.<sup>290</sup>

Before addressing Medicare coverage, it is important to remember that distribution of biologics is different than generic drugs. Currently, the vast majority of biologics are administered at doctor offices and

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285. E.g., INESSS, *supra* note 69, at 35–37.

286. INDUS. STANDARD RSCH., ASBM EUROPEAN PRESCRIBERS SURVEY 90 (2019).

287. A. Teeple, S. Ginsburg, L. Howard, L. Huff, C. Reynolds, D. Walls, L.A. Ellis, & J.R. Curtis, *Patient Attitudes About Non-Medical Switching to Biosimilars: Results From an Online Patient Survey in the United States*, 35 CURRENT MED. RSCH. & OP. 603, 606 (2019).

288. *Id.* at 606, 607 fig.4. However, a roughly equal percentage asserted that the new biologic did a better job treating their disease. *Id.* at 607 fig.4.

289. Elaine Nguyen, Erin R. Weeda, Diana M. Sobieraj, Brahim K. Bookhart, Catherine Tak Piech, & Craig I. Coleman, *Impact of Non-Medical Switching on Clinical and Economic Outcomes, Resource Utilization and Medication-Taking Behavior: A Systematic Literature Review*, 32 CURRENT MED. RSCH. & OP. 1281, 1283 (2016) (finding that patients whose conditions were stable had negative or neutral outcomes in terms of resource utilization or drug costs); Erin R. Weeda, Elaine Nguyen, Silas Martin, Michael Ingham, Diana M. Sobieraj, Brahim K. Bookhart, & Craig I. Coleman, *The Impact of Non-Medical Switching of Ambulatory Patients: An Updated Systematic Literature Review*, 7 J. MKT. ACCESS & HEALTH POL'Y, Oct. 2019, at 11–14; Olivia S. Costa, Tabassum Salam, Amy Duhig, Arati A. Patel, Ann Cameron, Jennifer Voelker, Brahim Bookhart, & Craig I. Coleman, *Specialist Physician Perspectives on Non-Medical Switching of Prescription Medications*, 8 J. MKT. ACCESS & HEALTH POL'Y, Mar. 9, 2020, at 8 (finding negative or neutral patient outcomes).

290. Jinoos Yazdany, *Failure to Launch: Biosimilar Sales Continue to Fall Flat in the United States*, 72 ARTHRITIS & RHEUMATOLOGY 870, 871 (2020).

hospitals.<sup>291</sup> For any treatment dispensed at a doctor office, there is no potential for automatic substitution by a pharmacist because no pharmacist is involved.<sup>292</sup> So, the usual structural mechanism of automatic pharmacy substitution of a generic for reducing costs simply does not exist. Moreover, health-care providers tend to purchase biologics in bulk and only later obtain reimbursement for actual use, which provides an incentive to maintain the status quo of continuing to use the originator biologic that they have already purchased.<sup>293</sup> Even though a doctor could theoretically purchase biosimilars in the next bulk purchase, financial incentives work against doing so because doctors are reimbursed based on the drug's average sales price plus a percentage. However, the average sales price does not account for frequent discounts only provided by originator biologics, such that doctors are compensated more for originator biologics.<sup>294</sup> In addition, logistical issues favor continuing with the status quo; doctors have stated that it is not convenient to keep both the originator and biosimilar on hand especially given that biologics, unlike traditional drugs, may have unique storage needs like specific temperatures.<sup>295</sup> Also, even if a doctor wanted to switch all patients to a biosimilar, it would require unreimbursed time to explain the change to the patient.<sup>296</sup>

The Medicare pricing scheme for biologics sold from pharmacies also disincentives use of biosimilars in a manner different than generics. First, for biosimilars distributed in health-care settings, there are separate reimbursement codes and prices, unlike generics that share the same codes

291. *E.g.*, BRILL, *supra* note 6, at 5; Makurvet, *supra* note 6, at 4–5.

292. *See* Afzali et al., *supra* note 66, at 2078 tbl.1 (“Auto-substitution [is the] practice of replacing one product for another at the pharmacy-level without notifying or seeking the approval of the prescriber.”).

293. *See, e.g.*, NITZAN ARAD, MARIANNE HAMILTON LOPEZ, REBECCA RAY, SUSAN DENTZER, ADAM KROETSCH, MARK MCCLELLAN, & MARTA WOSIŃSKA, DUKE MARGOLIS CTR. FOR HEALTH POL’Y, REALIZING THE BENEFITS OF BIOSIMILARS: WHAT THE U.S. CAN LEARN FROM EUROPE 8–9; *see also* Cole Werble, *Medicare Part B*, HEALTH AFFS. Aug. 2017, at 2 (discussing “buy-and-bill” practice). Contrary to this “buy-and-bill” practice, some health-care providers engage in “white bag” practice where they are reimbursed solely for administering the product whereas a pharmacy handles acquisition and thus has different incentive structures; however, providers could still opt for the more familiar brand biologic. *E.g.*, SAYANTAN NIYOGI, NICHOLAS ADOLPH, & ARTEM PASHCHINSKIY, IQVIA, BIOSIMILARS IN THE U.S.: REIMBURSEMENT AND IMPACTS TO UPTAKE 3–4, 7 (2021).

294. *See* HENRY A. WAXMAN, BILL CORR, JEREMY SHARP, RUTH McDONALD, & KAHAARI KENYATTA, THE COMMONWEALTH FUND, GETTING TO LOWER PRESCRIPTION DRUG PRICES: THE KEY DRIVERS OF COSTS AND WHAT POLICYMAKERS CAN DO TO ADDRESS THEM 9 (Maggie Van Dyke ed., 2020); *see also* Paul B. Ginsburg & Stephen M. Lieberman, *Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward*, USC-BROOKINGS SCHAEFFER ON HEALTH POL’Y (Feb 10, 2021), <https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2021/02/10/medicare-payment-for-physician-administered-part-b-drugs/> (noting a problem with the current system and suggesting possible solutions). In addition, the majority of outpatient clinics that administer biologics are eligible for discounts through the 340 B program, but this system does not require that discounts be passed to payers or patients, such that there is an incentive to continue using the more expensive drug, such as originator biologics. Conti et al., *supra* note 216.

295. *See* Teeple, *supra* note 166, at 613 (finding over 72% of doctors already prescribing biologics note logistical problems); *see also* OMAR HAFEZ, MCKESSON LIFE SCIENCES, BIOSIMILARS – OVERCOMING PHYSICIAN BARRIERS TO ADOPTION IN CLINICS 1 (2019) (noting that doctors may resist biosimilars depending on if it creates more hassle for their practice and/or the patient).

296. *See* Yazdany, *supra* note 290, at 872.



as their related drug to drive price competition.<sup>297</sup> As noted in one study, the current Medicare reimbursement policy does not provide the same magnitude of price competition for biosimilars as for traditional drugs, resulting in excess payments of \$1.6 billion over four years.<sup>298</sup> Not only is there precedent in the United States based on traditional drugs, but other countries have found a similar approach successful in promoting greater use of lower cost biosimilars.<sup>299</sup>

Another issue that disincentivizes biosimilar use is that Medicare Part D plan sponsors transition from complete to minimal responsibility once individuals on Medicare reach a threshold of spending. When a patient spends enough on pharmacy drugs each year to reach the catastrophic phase, the primary financial burden (80%) switches to the federal government.<sup>300</sup> More expensive drugs, such as originator biologics, result in a patient reaching the catastrophic phase more quickly, at which point the Medicare Part D plan sponsors pay less.<sup>301</sup> This practice raises Medicare costs for the government and disincentivizes biosimilar use.<sup>302</sup> An increasing number of patients are entering the catastrophic phase with Medicare spending tripling from 2010 to 2019.<sup>303</sup>

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297. Ginsburg & Lieberman, *supra* note 294. It is currently unknown whether interchangeable biosimilars will share the same reimbursement code as the brand biologic.

298. Sean R. Dickson & Tyler Kent, *Association of Generic Competition with Price Decreases in Physician-Administered Drugs and Estimated Price Decreases for Biosimilar Competition*, 4 J. AM. MED. ASSOC. NETWORK OPEN, Nov. 2021, at 6.

299. *Id.* at 7 (citing JC Robinson & Q. Jarrion, *Competition from Biosimilars Drives Price Reductions for Biologics in the French Single Payer Health System*, 40 HEALTH AFFS. 1190, 1192 (2021)).

300. WAXMAN ET AL., *supra* note 294, at 11. However, patients still pay 5%. BIOSIMILARS COUNCIL, INCREASING PATIENT ACCESS TO BIOSIMILARS IN MEDICARE PART D 1 (2020).

301. Stacie B. Dusetzina, Rena M. Conti, Nancy L. Yu, & Peter B. Bach, *Association of Prescription Drug Price Rebates in Medicare Part D with Patient Out-of-Pocket and Federal Spending*, 177 JAMA INT'L MED. 1185, 1186 (2017) (noting that at this point, the plan pays 15% and patients pay 5%).

302. *See id.*

303. *E.g.*, Juliette Cubanski & Tricia Neuman, *Millions of Medicare Part D Enrollees Have Had Out-of-Pocket Drug Spending Above the Catastrophic Threshold Over Time*, KAISER FAMILY FOUND. fig.3 (July 23, 2021), <https://www.kff.org/medicare/issue-brief/millions-of-medicare-part-d-enrollees-have-had-out-of-pocket-drug-spending-above-the-catastrophic-threshold-over-time>.

Private insurance companies also tend to favor originator biologics over biosimilars,<sup>304</sup> contrary to their current practices with generics.<sup>305</sup> Insurance companies typically give preference to lower cost generics by offering a lower co-pay or, where there is no generic, by imposing a requirement that patients “fail first” on a particular brand that has negotiated with the insurer for preference.<sup>306</sup> However, in the biologics context, insurance companies have often preferred the originator over a biosimilar and even required patients to first fail on the originator before being given the biosimilar.<sup>307</sup> This could be due to rebates that sway formulary decisions. As of 2019, only 14% of the largest private insurance plans prefer biosimilars and more than 30% prefer the originator.<sup>308</sup> This is likely caused by self-interested originator biologic manufacturers using rebates to incentivize

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304. One caveat is that some insurance companies may prefer cancer biosimilars, which are some of the most expensive biosimilars. See Yang et al., *supra* note 89, at 80 (stating that qualitative interviews suggest that the majority of payors prefer biosimilars for patients new to monoclonal antibodies to treat cancer and that few of these were available at the time of the Chambers et al. study, *infra* note 305); Laura Joszt, *AMCP Nexus Survey: Two Thirds of Payers Use Biosimilars to Manage Oncology Drug Costs*, *AJMC* (Nov. 23, 2021), <https://www.ajmc.com/view/amcp-nexus-survey-two-thirds-of-payers-use-biosimilars-to-manage-oncology-drug-costs> (finding that among eleven payors covering 238 million patients, 67% preferred oncology biosimilars, generally due to the increasing cost of cancer care). *But see* Alice J. Chen, Priya Bhanot, Laura Gascue, Rocio Ribero, Rita Shane, & Karen Van Nuys, *Insurer Formularies Complicate the Adoption of Biosimilar Cancer Therapies*, *HEALTH AFFS.* (Apr. 8, 2021), <https://www.healthaffairs.org/doi/10.1377/forefront.20210405.345071/abs> (finding that for five major insurance providers that provide coverage for 40% of U.S. cancer patients, although biosimilars were interchangeable, there was no consensus on preferring the biologic or biosimilar version).

305. James Chambers, Rachel C. Lai, Nikoletta M. Margaretos, Ari D. Panzer, Joshua T. Cohen, & Peter J. Neumann, *Coverage for Biosimilars vs. Reference Products Among US Commercial Health Plans*, 323 *J. AM. MED. ASS'N* 1972, 1972 tbl.1 (2020). *But see* Mariana Socal, Ge Bai, & Gerard F. Anderson, *Favorable Formulary Placement of Branded Drugs in Medicare Prescription Drug Plans When Generics Are Available*, 179 *JAMA INTERNAL MED.* 832, 832 (2019) (finding that over 70% of formularies placed the brand product in a lower-cost sharing tier than at least one generic); James Schneider, *UnitedHealthcare, Cigna, Aetna, All Unveil New Policies Restricting Biologics Use*, *FYNE FETTLE* (July 29, 2021) (noting that some insurance companies are now requiring patients to switch to a biosimilar), <https://fynefettle.com/unitedhealthcare-cigna-aetna-all-unveil-new-policies-restricting-biologics-use>.

306. See Charles Ornstein & Katie Thomas, *Take the Generic Drug, Patients Are Told — Unless Insurers Say No*, *PROPUBLICA* (Aug. 6, 2017, 6:00 PM) <https://www.propublica.org/article/take-the-generic-drug-patients-are-told-unless-insurers-say-no>.

307. *E.g.*, AVALERE HEALTH, *USE OF STEP THROUGH POLICIES FOR COMPETITIVE BIOLOGICS AMONG COMMERCIAL US INSURERS* 8 (2018) (finding that more than half of plans with publicly available information require use of brand biologic Remicade first); WAYNE WINEGARDEN, *INCENTING COMPETITION TO REDUCE DRUG SPENDING: THE BIOSIMILAR OPPORTUNITY* 17 (2019) (noting that UnitedHealthcare prefers originator Neulasta rather than biosimilars); *see also* Laura Karas, *The Ongoing Step Therapy Debate*, *BILL OF HEALTH* (Apr. 19, 2021), <https://blog.petrieflom.law.harvard.edu/2021/04/19/step-therapy-pharma-biosimilars> (noting that the reintroduction of proposed federal legislation has revived debate about counterintuitive step therapy to mandate use of more expensive brand biologic first which can not only increase health-care costs, but may also lower medication adherence). Some of these requirements could be due to anticompetitive activity. *See generally* Van de Wiele et al., *supra* note 6 (discussing antitrust dispute regarding Remicade).

308. Chambers et al., *supra* note 305, at 1972 tbl.1; *see also* Chen et al., *supra* note 304 (finding that for five insurance providers that provide coverage for 40% of cancer patients, one preferred the brand biologic, one preferred biosimilars, and two covered both equally, although also noting that plans can and do change coverage preferences); Sean McGowan, *Five Years on, Biosimilars Need Support from All Health Care Players*, *STAT* (Mar. 6, 2020), <https://www.statnews.com/2020/03/06/biosimilars-in-us-turn-five> (noting that UnitedHealthcare favors only some brand biologics likely due to rebates).

payors to prefer their biologic.<sup>309</sup> Given that the rebates can be 50% of the list price, it may be cheaper for the payor to prefer the originator rather than a biosimilar.<sup>310</sup> As some have noted, unless a substantial number of patients switch to a biosimilar, the rebates make it less profitable for payors to promote a biosimilar.<sup>311</sup> This practice seems less common for nonbiologic drugs, potentially because the larger price differential for generics disincentivizes remaining with the brand.

### C. How Cognitive Biases Promote Bias Against Biosimilars

This Section explains why marketing has been successful in establishing and perpetuating bias against biosimilars due to common cognitive biases, such as loss aversion bias, availability bias, and confirmation bias. Moreover, given inherent ambiguity with regulatory approval of biosimilars, these biases are especially likely to proliferate to address the ambiguity. Understanding how these individual biases make doctors and patients gullible to marketing is important to gauge the strength of existing biases and to determine appropriate solutions.

#### 1. Loss Aversion Bias and Availability Bias

The marketing previously discussed could easily cause availability bias in favor of originator biologics and trigger loss aversion bias. For example, consider that originator biologics are marketed for a minimum of twelve years before a biosimilar can be approved.<sup>312</sup> During this time, only the originator biologic is available and marketed.<sup>313</sup> So, for example, the originator biologic Remicade was advertised and used by patients for more than a dozen years before the first biosimilar started to be marketed.<sup>314</sup>

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309. See Hakim & Ross, *supra* note 230, at 2163; see also Karas, *supra* note 307; Benjamin Hayes, *Cats at the Christening: Bundled Rebates, Doctrinal Blind Spots, and the Risks of Antitrust Under-Enforcement in the Biologic Pharmaceutical Market*, 51 U. MEMPHIS L. REV. 917, 931–32, 950 (2021); FTC, REPORT ON REBATE WALLS 2–5 (2021) (discussing how rebates incentivize higher priced drugs and antitrust implications), [https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-report-rebate-walls/federal\\_trade\\_commission\\_report\\_on\\_rebate\\_walls.pdf](https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-report-rebate-walls/federal_trade_commission_report_on_rebate_walls.pdf); Joanna Shepherd, *Pharmacy Benefit Managers, Rebates and Drug Prices: Conflicts of Interest in the Market for Prescription Drugs*, 38 YALE L. & POL'Y REV. 357, 391–94 (2019) (discussing different ways to tackle rebates including eliminating them altogether as well as requiring partial pass through of benefits).

310. See Hakim & Ross, *supra* note 230, at 2163. Moreover, rebates increased by over 50% from 2012 to 2016. PEW CHARITABLE TRUSTS, THE PRESCRIPTION DRUG LANDSCAPE EXPLORED: A LOOK AT RETAIL PHARMACEUTICAL SPENDING FROM 2012 TO 2016 40 (2019).

311. See Hakim & Ross, *supra* note 230, at 2163. This has been referred to as a “rebate trap” given insurers prefer the brand biologic with a higher list price because it is cheaper for the insurer to do so. *Id.* Some companies enter into multiyear rebate agreements immediately before a biosimilar launch. See Yazdany, *supra* note 290, at 871.

312. See 42 U.S.C. § 262(k)(7)(A).

313. See *id.*

314. Remicade was first approved in the United States in 1998. See REMICADE (INFLIXIMAB) LABEL, JANSSEN BIOTECH, INC. 1 (2013), <https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf>. Although the FDA approved a biosimilar in 2016, it was not marketed until 2017. *E.g.*, Stacy Elder Dalpoas, Mariana Social, Celia Proctor, & Kenneth M. Shermock, *Barriers to Biosimilar Utilization in the United States*, 77 AM. J. HEALTH-

When availability bias is combined with loss aversion bias, serious resistance to change likely results. After all, loss aversion bias disproportionately overvalues possible loss.<sup>315</sup> A patient who has been taking Humira for more than a decade might assume there would be worse outcomes from a biosimilar after seeing advertisements that suggest switching to a biosimilar is unsafe. Even an advertisement that stated the scientifically accurate fact that biosimilars are not identical could exacerbate loss aversion bias; this is especially true if the patient is already biased against generics, as many are.<sup>316</sup> These implications are consistent with studies indicating patients are more reluctant to switch to biosimilars if they were treated longer with the originator biologic.<sup>317</sup>

Moreover, those with a bias against biosimilars may, through confirmation bias, improperly interpret evidence and then further propagate bias by spreading incorrect information to others. For example, Andrew Spiegel, the leader of the Global Colon Cancer Association, is a noted patient advocate who has made repeated statements questioning the safety of biosimilars in Europe,<sup>318</sup> contrary to actual findings of scientists concerning their safety.<sup>319</sup> Because patients are likely to encounter views of patient advocates such as Spiegel on patient-oriented websites, his inaccurate views are highly available to existing patients.<sup>320</sup> Moreover, a patient who has been taking an originator biologic for a decade is likely to view the false statements from Spiegel as true due to loss aversion bias.

## 2. High Ambiguity Promotes Confirmation Bias

Existing bias against biosimilars may be exacerbated by confirmation bias occurring in situations of high ambiguity such as biosimilar science and regulatory approval.<sup>321</sup> Although there are multiple systematic reviews supporting the safety and efficacy of switching to a biosimilar, some with

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SYS. PHARMACISTS 2006, 2007 tbl.1(2020); *see also* AMGEN BIOSIMILARS, 2021 BIOSIMILAR TRENDS REPORT 11 fig.3 (2021), [https://www.amgenbiosimilars.com/commitment/-/media/Themes/Amgen/amgenbiosimilars-com/Amgenbiosimilars-com/pdf/USA-CBU-80962\\_Amgen-2021-Biosimilar-Trends-Report.pdf#page=11](https://www.amgenbiosimilars.com/commitment/-/media/Themes/Amgen/amgenbiosimilars-com/Amgenbiosimilars-com/pdf/USA-CBU-80962_Amgen-2021-Biosimilar-Trends-Report.pdf#page=11) (showing timeline of FDA approval versus launch of biosimilars).

315. *See supra* notes 137–40 and accompanying text (discussing loss aversion).

316. *See* discussion *supra* Section I.C.2 (describing patient bias against generics).

317. *See* Scherlinger et al., *supra* note 197, at 929 (finding that the majority of those who refused to switch to a biosimilar had been treated with the originator for seven versus four years on average).

318. *See Public Hearing on Facilitating Competition and Innovation in the Biological Products Marketplace, Part 15: Hearing Before the Food & Drug Admin.* 193–94, 197–99 (2018) (statement of Andrew Spiegel, Global Colon Cancer Ass'n). Spiegel also cofounded Alliance for Safe Biologic Medicines, which often raises concerns about switching biosimilars due to cost. *See id.* at 194; *see also* Patients, Physicians Raise Concerns with BC Biosimilar Non-Medical Switching Policy, ALL. FOR SAFE BIOLOGIC MEDS. (June 6, 2019) <https://safebiologics.org/2019/06/patients-physicians-raise-concerns-with-bc-biosimilar-non-medical-switching-policy>.

319. *E.g.*, BIOSIMILARS FORUM, *supra* note 81, at 8; EUR. MEDS. AGENCY & EUR. COMM'N, *supra* note 66, at 24; Eduardo Cazap, Ira Jacobs, Ali McBride, Robert Popovian, & Karol Sikora, *Global Acceptance of Biosimilars*, 23 ONCOLOGIST 1188, 1194 (2018).

320. *See, e.g.*, Andrew Spiegel, *Patient Safety is Essential for New Cancer Meds*, PENNLIVE (Mar. 23, 2019, 4:16 PM), [https://www.pennlive.com/editorials/2011/08/patient\\_safety\\_is\\_essential\\_fo.html](https://www.pennlive.com/editorials/2011/08/patient_safety_is_essential_fo.html) (discussing the safety of biosimilars in a skeptical fashion).

321. *E.g.*, *Dangerous Concoction*, *supra* note 119, at 805.

a bias against biosimilars might focus on arguable ambiguity to perpetuate that bias.<sup>322</sup> For example, although the vast majority of studies support switching to biosimilars, there are two out of ninety studies that found possible safety issues that could provide enough ambiguity for those with confirmation bias to view as proof of safety problems.<sup>323</sup> Some reviews have noted that studies to date do not provide robust evidence, again creating ambiguity that could promote confirmation bias against biosimilars.<sup>324</sup> Sometimes even a systematic review that finds no statistical differences on safety or efficacy will nonetheless suggest that the studies do not provide robust evidence because there is inadequate long-term data.<sup>325</sup> This suggestion could simply be a cautious statement by a scientist. However, someone with an existing bias against biosimilars may view this as evidence confirming that biosimilars are not safe. Similarly, someone biased against biosimilars that reads a conclusion that studies show safety and efficacy concerns are a “low risk” in the “great majority” of switching studies may remain skeptical based on confirmation bias, especially if there are limited studies.<sup>326</sup>

Confirmation bias also likely plays a role in the interpretation of studies of, and policies regarding, the switching of patients to biosimilars.

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322. See sources cited *supra* note 279. There are some studies that conclude that switching for nonmedical reasons such as cost is generally safe and effective. *E.g.*, Bernard et al., *supra* note 181, at 2355, 2359; see also Ahmad Zainal Abidin, Centaine L. Snoswell, Leila Shafiee Hanjani, Gavin Callaghan, & Michelle Edmonds, *Infliximab Switching from Reference Product to Biosimilar: A Review of Evidence Regarding the Clinical Efficacy, Safety Profile and Immunogenicity*, 51 *J. PHARMACY PRAC. & RSCH.* 358, 371 (2021) (review establishing ever-increasing evidence of safety in switching).

323. See Cohen et al., *supra* note 277, at 464, 471, 475; see also Stanton Mehr, *More Clinical Evidence that Biosimilar Switching Carries Low Risk*, *BIOSIMILARS REV. & REP.* (Mar. 6, 2018), <https://biosimilarsr.com/2018/03/06/clinical-study-evidence-biosimilar-switching-carries-low-risk> (discussing Cohen et al. article and findings).

324. See Brian G. Feagan, Gordon Lam, Christopher Ma, & Gary R. Lichtenstein, *Systematic Review: Efficacy and Safety of Switching Patients Between Reference and Biosimilar Infliximab*, 49 *ALIMENTARY PHARMACOLOGY THERAPEUTICS* 31, 37 (2019) (concluding that evidence is weak with only the NOR-SWITCH study reporting on the noninferiority of switching and that different patient groups may also have different responses); see also Brian G. Feagan, Mona Marabani, Jashin J. Wu, Freddy Faccin, Claire Spronk, & Gilberto Castañeda-Hernández, *The Challenges of Switching Therapies in an Evolving Multiple Biosimilars Landscape: A Narrative Review of Current Evidence*, 37 *ADVANCES THERAPY* 4491, 4509 (2020) (concluding that evidence is inadequate because it is mostly based on real-world studies that are not empirically robust); Ross A. McKinnon, Matthew Cook, Winston Liauw, Mona Marabani, Ian C. Marschner, Nicolle H. Packer, & Johannes B. Prins, *Biosimilarity and Interchangeability: Principles & Evidence: A Systematic Review*, 32 *BIODRUGS* 27, 45 (2018) (reviewing fifty-seven switching studies and finding that the majority reported nonstatistically significant differences on efficacy, although noting that there is a lack of robustness of evidence and limited long-term data because only eight studies evaluated beyond one year). In addition, although there are extensive studies of switching to biosimilar infliximab, given fewer studies available for areas such as oncology, this could be viewed as a point of ambiguity. See Ebbers & Schellekens, *supra* note 203, at 1964 (noting that data is mostly available for infliximab switching and not for other products, such as those used in oncology).

325. See McKinnon et al., *supra* note 324, at 27 (focusing on observational studies that lack information on immunogenicity and inadequate powering within all diagnostic groups as revealing evidence gaps); Zoltán Szekanez, *Biosimilars: To Switch or Not to Switch—That is the Question*, 58 *REUMATOLOGIA*, Jan. 2020, at 1–2 (suggesting that there is no medical reason to switch and that there remains inadequate real-world data on nonmedical switching).

326. See Cohen et al., *supra* note 277, at 464 (citing Keypoints discussion).

There is real-world evidence, including more than a decade of biosimilar use in Europe and multiple medical society and domestic health agency recommendations, in favor of switching.<sup>327</sup> Also, a number of medical societies have modified their positions over time in favor of switching.<sup>328</sup> Nonetheless, because there is not complete agreement in favor of switching, the ambiguity prompts confirmation bias in those with existing bias against biosimilars, directing focus on the minority of statements that do not recommend switching.

Additional ambiguity exists around the regulatory approval process for biosimilars that could unduly promote skepticism and bias against biosimilars. For example, the regulatory approval standard of highly similar for biosimilars is more ambiguous than an identical active ingredient that is bioequivalent (for generics), even if deemed to be as safe and effective as the originator.<sup>329</sup> The approval process for biosimilars can also be characterized as ambiguous. In particular, whereas every generic application involves the same standard process, the FDA review of biosimilars is individually tailored in terms of what type of evidence is required.<sup>330</sup> Although the biosimilar review process is intended to provide flexibility given inherent scientific complexities with biologics that do not exist with traditional drugs, this flexibility injects ambiguity that promotes bias. An additional layer of ambiguity promoting confirmation bias is the FDA policy to permit a biosimilar manufacturer to gain approval for some indications based on extrapolation from evidence of one indication.<sup>331</sup> Indeed, some doctors have expressed concern about biosimilars approved for

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327. *E.g.*, Edwards et al., *supra* note 201, at 1008 (“The European Crohn’s and Colitis Organization, various national rheumatology societies and the British Association of Dermatology have all expressed support for prescriber-initiated switching.”); CADTH, INTERNATIONAL POLICIES ON THE APPROPRIATE USE OF BIOSIMILAR DRUGS 7–8 (2018) (noting that the UK, Germany, France, Netherlands, Norway, Finland, Australia, and New Zealand health agencies all consider it safe to switch to biosimilars); Jonathan Kay, Monika M. Schoels, Thomas Dörner, Paul Emery, Tore K. Kvien, Josef S. Smolen, & Ferdinand C. Breedveld, *Consensus-Based Recommendations for the Use of Biosimilars to Treat Rheumatological Diseases*, 77 ANNALS RHEUMATIC DISEASES 165, 165 (2018) (citing consensus of an international panel of rheumatologists around the safety of switching).

328. Several groups changed their position within just a few years to favor biosimilars from either prior opposition or waiting for more information. *See* MEDICINES FOR EUROPE, *supra* note 228, at 19–21 (noting the positions of several groups and potential changes they endorse).

329. *See* discussion *supra* Section I.A.2 (discussing biosimilar regulatory standard); *see also* John R.P. Tesser, Daniel E. Furst, & Ira Jacobs, *Biosimilars and the Extrapolation of Indications for Inflammatory Conditions*, 11 BIOLOGICS: TARGETS & THERAPY 5, 8 (2017) (noting that regulatory approval of biosimilars is based on totality of evidence, such that there is a great deal of interpretation).

330. *See* *Biosimilar Development, Review and Approval*, FDA, <https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval#types> (last visited Mar. 21, 2022).

331. *See* HHS, FDA, CDER, & CBER4, SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY 21 (2015). The EU also follows the same practice. EMA COMM. FOR MED. PRODS. FOR HUMAN USE, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NONCLINICAL AND CLINICAL ISSUES, 12 (2015). The ambiguity inherent with extrapolation is underscored by the fact that agencies can come to different conclusions based on the same evidence. *E.g.*, Tesser et al., *supra* note 329, at 8 (noting that regulatory agencies in fact have come to different conclusions); *see also* Andriy Krendyukov & Martin Schiestl, *Extrapolation Concept at Work with Biosimilar: A Decade of Experience in Oncology*, 3 ESMO OPEN 1, 1 (2018) (noting that extrapolation is “most commonly misunderstood”).

indications based on extrapolations, rather than affirmative data,<sup>332</sup> with a significant number believing that it should never be appropriate.<sup>333</sup> However, extrapolation is consistent with legal and scientific principles,<sup>334</sup> essential to making biosimilar regulatory approval cost-effective,<sup>335</sup> and ethically supported to ensure that patients are not subjected to unnecessary tests.<sup>336</sup> Nonetheless, the term extrapolation itself may have improper connotations.<sup>337</sup>

Due to confirmation bias, somewhat ambiguous, neutral statements by health-care professionals may be negatively perceived by a patient that has an existing bias against biosimilars. For example, consider a likely scenario where a patient is told that a biosimilar “may” help, which is true of all medications. A patient who is already biased against biosimilars will inappropriately assume the biosimilar is less effective due to the bias against biosimilars compounded by confirmation bias which causes the patient to interpret all facts consistent with biased beliefs. Of course, even if a patient is told that the biosimilar “is likely” to help, a patient who has a strong bias against biosimilars may cling to the fact that there is no guarantee that the biosimilar will help. In either event, statements by health-care professionals can unintentionally prompt nocebo effects, which will result in further confirmation bias against biosimilars.<sup>338</sup>

#### IV. ADDRESSING BIAS AGAINST BIOSIMILARS

##### A. The Challenge of Changing Beliefs

Identifying that there is a problem is only the first step to a solution. This Section briefly explains why biases against biosimilars can be difficult to overcome. Nonetheless, there is reason for optimism. While changing beliefs is challenging, sometimes desired behavior can be nudged

332. E.g., Hemmington et al., *supra* note 183, at 574 (finding that 32% of surveyed New Zealand doctors in specialties that prescribe biologics were not confident about the indications of extrapolation); Samola et al., *supra* note 178, at 16–17 (noting extrapolation is an issue noted in studies concerning biosimilar disadvantages). *But see* Yang et al., *supra* note 89, at 10 (noting that among surveyed oncologists who had previously prescribed biologics, most were comfortable with extrapolated indications).

333. See Eline van Overbeeke, Birgit De Beleyr, Jan de Hoon, Rene Westhovens, & Isabelle Huys, *Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists*, 31 *BIOLOGICS* 447, 452–53 (2017) (39% of Belgian rheumatologists surveyed suggested it was never appropriate to extrapolate indications).

334. E.g., Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 *DUKE L. J.* 377, 379–80 (2014) (discussing use of extrapolation not only for biosimilars, but also for off-label uses, new subpopulations of patients, and new doses); Krendyukov & Schiestl, *supra* note 331, at 1.

335. Gareth P. Gregory, Christine Carrington, Chan Y. Cheah, Eliza A. Hawkes, Ian M. Ivring, Jim Siderov, & Stephen Opat, *A Consensus Statement on the Use of Biosimilar Medicine in Hematology in Australia*, 16 *ASIA-PAC. J. CLINICAL ONCOLOGY* 211, 218 (2020).

336. *Id.*

337. See Krendyukov & Schiestl, *supra* note 331, at 1. In fact, Canada removed use of this term in its guidance document and instead uses the term “authorization of indications” of the biosimilar. HEALTH CAN., *GUIDANCE DOCUMENT: INFORMATION AND SUBMISSION REQUIREMENTS FOR BIOSIMILAR BIOLOGIC DRUGS* 19–20 (2016).

338. Rezk & Pieper, *supra* note 201, at 212; Luana Colloca & Damien Finniss, *Nocebo Effects, Patient-Clinician Communication and Therapeutic Outcomes*, 307 *JAMA* 567, 567 (2012).

through structural changes. This Section documents eventual successful use of generics in the United States as well as some successful biosimilar use in the United States despite biases.

### 1. Why Biases Are Hard to Change

A major issue with addressing bias against biosimilars is that biases can be difficult to change. Studies show attempts to correct misinformation may actually result in people incorrectly remembering the discredited information as truth.<sup>339</sup> This could be because the correction repeats the prior wrong information and makes that information more available than the new information.<sup>340</sup> Even when a correction has some success, it tends to be partial; for example, after false advertisements that Listerine “prevents colds,” corrective advertising only slightly reduced beliefs concerning this inaccurate information.<sup>341</sup> Moreover, studies show that attempts to correct misperceptions can backfire and instead strengthen initial beliefs.<sup>342</sup> This result is consistent with the previously discussed concept of confirmation bias, which reinforces existing views.

Although correcting biases can be challenging, there is reason for hope in addressing bias against biosimilars. First, studies indicate that corrections are more likely to be successful concerning issues of health than other issues like politics.<sup>343</sup> Of course, this is only true if the health issue is not associated with partisan identities, such as a predominant view among some conservatives that masks are ineffective in protecting against COVID-19 infections, contrary to scientific data.<sup>344</sup> However, not all public health issues are tied to politics and views on drugs can change—doctors and patients alike have an increasingly accurate perception of generic drugs.<sup>345</sup> Second, corrections are more likely to succeed if an alternative and coherent explanation is provided, including potentially a reason for the original bias.<sup>346</sup> For example, simply stating that vaccines are safe is

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339. E.g., John M. Carey, Victoria Chi, D. J. Flynn, Brendan Nyhan, & Thomas Zeitzoff, *The Effects of Corrective Information About Disease Epidemics and Outbreaks: Evidence from Zika and Yellow Fever in Brazil*, 6 SCI. ADVANCES, Jan. 2020, at 8 (finding that corrected information disappeared after a delay).

340. See *supra* notes 120–26 and accompanying text (discussing availability bias).

341. Lewandowsky et al., *supra* note 15, at 107.

342. See, e.g., *id.* at 119. As one example, campaigns to reduce smoking may potentially lead to an increase in smoking. *Id.*

343. Nathan Walter & Sheila T. Murphy, *How to Unring the Bell: A Meta-Analytic Approach to Correction of Misinformation*, 85 COMM’N MONOGRAPHS 423, 436 (2018). This likely helps explain why some conservatives continue to believe President Obama is not a U.S. citizen; the debunked information is political. Brendan Nyhan & Jason Reifler, *When Corrections Fail: The Persistence of Political Misperceptions*, 32 POL. BEHAV. 303, 323 (2010).

344. See, e.g., Toni G.L.A. van der Meer & Yan Jin, *Seeking Formula for Misinformation Treatment in Public Health Crises: The Effects of Corrective Information Type and Source*, 35 HEALTH COMM’N 560, 568–69 (2020); Ryan Lizza & Daniel Lippman, *Wearing a Mask is for Smug Liberals. Refusing for Reckless Republicans*, POLITICO (May 5, 2020, 4:30 AM), <https://www.politico.com/news/2020/05/01/masks-politics-coronavirus-227765>.

345. See, e.g., *supra* note 141 and accompanying text (noting change in perspectives from 2011 to 2016).

346. Lewandowsky et al., *supra* note 15, at 117.



not as helpful as explaining how the misconception that they cause autism began.<sup>347</sup> However, providing an alternative story is tricky because studies show that individuals tend to believe simple and persuasive stories, which reflects pharmaceutical marketing that focuses on simple, albeit inaccurate, stories.<sup>348</sup> Nonetheless, given that consumers broadly recognize that generics are safe and a better value, it is possible to recognize the value of lower cost, high quality drugs, even if there might be some lingering bias against them.

Researchers have proposed guidelines to directly address misinformation. First, education with correct information needs to avoid repetition of misinformation (i.e., the common myth versus fact formula is not helpful because it may simply reinforce the misinformation).<sup>349</sup> Second, the correct information needs a strong narrative because compelling stories are better remembered.<sup>350</sup> Also, presenting the correct information in a way that affirms an individual's world view is ideal; this can be tricky with biosimilars because patients often assume more expensive products are better.<sup>351</sup> However, unlike generics that are usually much cheaper than the brand version, biosimilars are still typically quite expensive.<sup>352</sup> In addition, some researchers have suggested moving beyond direct refutation of misinformation to include peer pressure and structural nudges.<sup>353</sup> For example, opposition to climate change does not matter if there are structural nudges to incentivize climate-friendly behavior, such as tax credits for electric cars. And, as discussed next, the dominant use of generics in the United States is likely a function of structural nudges in the form of laws as well as private payor policies.<sup>354</sup>

## 2. Structural Changes Can Nudge Desired Action Despite Lingering Biases

This Section provides examples of how structural changes can successfully improve desired usage and dissipate biases. It shows how U.S. generic use has dramatically increased despite some continued bias. It also provides examples of how structural changes in Europe and in some limited situations in the United States have successfully promoted biosimilar use.

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347. *See id.* (providing example that suspected weapons of mass destruction (WMD) sites in Iraq were actually grain silos would be ineffective since it would not explain *why* initial reports suspected the sites housed WMDs).

348. *See id.*

349. *Id.* at 122–23.

350. *See, e.g., Drugged Out, supra* note 116, at 445–46.

351. Lewandowsky et al., *supra* note 15, at 123; Schmidt et al., *supra* note 149, at 1.

352. *See, e.g.,* Beth Snyder Bulik, *Biosimilars Versus Biologics: Is Marketing Madness on the Way as Biosimilar Approvals Balloon?*, FIERCE PHARMA (Aug. 16, 2021, 4:17 PM), <https://www.fiercepharma.com/marketing/biosimilar-or-biologic-marketing-madness-way-as-bio-similar-approvals-balloon>.

353. Lewandowsky et al., *supra* note 15, at 124.

354. *See* discussion *infra* Section IV.A.2

## a. History of Generics in the United States

The history of generic drug use in the United States shows that structural changes to laws and policies can increase generic use and change personal views. Widespread generic use that happens promptly after generics enter the market is often attributed to state laws that permit or even require generic substitution.<sup>355</sup> However, in an earlier era, most states had laws banning generic substitution because of a massive misinformation campaign initiated by pharmaceutical companies.<sup>356</sup> The dramatic change from banning generic substitution to actively encouraging it was prompted in large part by newly enacted Medicare and Medicaid laws that created a financial incentive to reduce costs.<sup>357</sup> In addition, anti-substitution laws created practical and economic burdens in terms of keeping all brand drugs in stock.<sup>358</sup> By 1971, the national lobbying group for pharmacists, in conjunction with AARP and organized labor, took a firm stand against anti-substitution laws that included efforts to educate patients and change state laws.<sup>359</sup> In 1973, Medicaid reimbursements for drugs were set to the price of generics unless there was a demonstrated difference in therapeutic effect.<sup>360</sup> The Medicaid reimbursement policy is consistent with hospitals' prior successful use of formularies (lists of covered drugs) to promote use of cheaper generics—even during the era of anti-substitution laws that could override doctor preferences because doctors were required to consent to the formulary as a condition of treating patients at the hospital.<sup>361</sup> By 1984, anti-substitution laws were successfully repealed.<sup>362</sup>

However, repealing anti-substitution laws was only the first step toward increasing generic use because views of doctors and patients still needed to change. Initially, doctors resisted substitution with generics; the American Medical Association (AMA) passed a resolution in 1975 urging doctors to consistently bar pharmacy dispensation of generics by indicating that the prescription should be dispensed as written, apparently at the suggestion of drug companies appealing to doctors valuing their autonomy.<sup>363</sup> Around the same time, some grocery stores advertised drug prices

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355. Typically, within a month of generic market entry the generic will account for 90% of dispensed prescriptions. *See, e.g.*, Marta Wosinska & Robert S. Huckman, *Generic Dispensing and Substitution in Mail and Retail Pharmacies*, 23 HEALTH AFF. 409, 413 (2004).

356. JEREMY A. GREENE, *GENERIC: THE UNBRANDING OF MODERN MEDICINE* 139–40 (2014); *see also* Neil J. Facchinetti & W. Michael Dickson, *Access to Generic Drugs in the 1950s: The Politics of a Social Problem*, 72 AM. J. PUB. HEALTH 468, 473–74 (1982) (discussing the need to bar generic substitution as an engineered social crisis).

357. GREENE, *supra* note 356, at 151.

358. *Id.* at 141 (discussing substitution bars as creating challenges for pharmacists).

359. *Id.* at 147–49. Pharmacists had previously supported bars for substitution of drugs but changed their stance once more stringent federal laws made counterfeit drugs no longer a problem. *See, e.g.*, Hossein Salehi & Stuart O. Schweitzer, *Economic Aspects of Drug Substitution*, 6 HEALTH CARE FIN. REV. 59, 59–60 (1985).

360. GREENE, *supra* note 356, at 152.

361. *Id.* at 151 (noting that generics helped reduce costs and manage inventory).

362. *Id.* at 155.

363. *Id.* at 195.

and even took out ads promoting generics.<sup>364</sup> Despite these efforts, most patients in 1980 did not request generics, and doctors and pharmacists were still reluctant to prescribe and dispense them.<sup>365</sup> A survey in the mid-1980s found that most patients were familiar with the term generic and 20% erroneously believed that generics were lower quality than brand drugs.<sup>366</sup>

Generic use has increased over the decades,<sup>367</sup> likely due to increased knowledge of their equivalent safety and efficacy, as well as several financial incentives.<sup>368</sup> First, a 1984 change to regulatory laws expedited approval of generics, which lowered the cost of generic entry and substantially increased the number of generics in the market<sup>369</sup> with increased competition resulting in lower prices. Lower priced generics promoted substitution by pharmacists because their profit margin was higher with generics than brand name drugs.<sup>370</sup> In addition, although some doctors and patients may retain illogical biases against generics, today only about 5% of prescriptions are written as “do not substitute,” which contrasts sharply with the 1975 AMA position urging doctors to oppose all generics.<sup>371</sup> Some of this could be due to payor pressure to use generics; starting in the early 1990s, insurers began using formularies to exclude coverage of expensive brands.<sup>372</sup> By the 2000s, private insurers further promoted generics with tiered formularies that included greater cost differentials between generics and brands, which could result in a twofold difference in price.<sup>373</sup>

#### b. How the United States Can Learn from Other Countries and Contexts

There is also direct evidence of how existing structures can promote biosimilar use. Europe is an obvious place to consider because it accounts

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364. *Id.* at 198.

365. *Id.* at 203.

366. *Id.* at 206.

367. See, e.g., Scott Gottlieb, *Don't Give Up on Biosimilars—Congress Can Give Them a Boost*, WALL ST. J. (Aug. 25, 2019), <https://www.wsj.com/articles/I-give-up-on-biosimilarscongress-can-give-them-a-boost-11566755042> (noting that generics were only 36% of drugs in 1994, then about 75% in 2009, and 87% in 2015).

368. As discussed earlier, the vast majority of patients now agree that generics are safe and effective, whereas in the mid-1980s, about 20% believed that generics were lower quality. GREENE, *supra* note 356, at 206.

369. 21 U.S.C. § 355(j); CBO, HOW INCREASED GENERIC COMPETITION HAS AFFECTED DRUG PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 27–28 (1998).

370. See Elyse Tanouye, *Price Markups on Generics Can Top Brand-Name Drugs*, WALL ST. J. (Dec. 31, 1998, 12:01 AM), <https://www.wsj.com/articles/SB915062993167849000>.

371. William H. Shrank, Joshua N. Liberman, Michael A. Fischer, Jerry Avorn, Elaine Kilabuk, Andrew Chang, Aaron S. Kesselheim, Troyen A. Brennan, & Niteesh K. Choudhry, *The Consequences of Requesting “Dispense as Written,”* 124 AM. J. MED. 309, 313 (2011). A 2005 study revealed that three-quarters of physicians permit generic substitution. BARRETT, *supra* note 143, at 7.

372. GREENE, *supra* note 356, at 232.

373. Teresa B. Gibson, Ronald J. Ozminkowski, & Ron Z. Goetzel, *The Effects of Prescription Drug Coverage: A Review of the Evidence*, 11 AM. J. MANAGED CARE 730, 730 (2005) (noting that in 2005, a review of the literature indicated that most payors had moved from two-tier plans to three-tier plans).

for 90% of global biosimilar sales.<sup>374</sup> However, many structural policies used in Europe to promote biosimilars such as mandating that biosimilars have lower prices, nationwide purchasing of lower cost biosimilars, quotas on individual doctors, and sometimes mandating biosimilar use are anathema to U.S. practices.<sup>375</sup> Accordingly, this Section focuses on aspects of European structures that promote biosimilar use, as well as a couple of niche U.S. situations with very strong biosimilar use.

i. European Structural Policies that Promote Biosimilar Use

Studies in Europe suggest that ideally biosimilar use is promoted by multiple incentives. Germany, which has the most policies favoring biosimilars, has the highest biosimilar usage.<sup>376</sup> Although some policies such as prescription quotas and penalties would not apply to the United States, there are nonetheless other structural policies that could be adopted, including financial incentives and gentle nudges such as prescription guidelines and education.

One structural nudge used in Europe involves policies directed at patients that create a financial incentive to choose biosimilars. In several European countries, cost-effective biosimilars are promoted by requiring patients to pay the difference between the brand and biosimilar.<sup>377</sup> This somewhat mirrors what U.S. insurers already do with coverage of generics in terms of lower co-pays.<sup>378</sup> However, even in Europe, this strategy alone was not entirely successful because the originator biologic manufacturers sometimes reduced their prices immediately before biosimilar entry.<sup>379</sup> This highlights the problem of relying on a single strategy to promote biosimilar use.

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374. BIOSIMILARS FORUM, *supra* note 81, at 6. The authors note that Europe admittedly has fewer patent and anticompetitive barriers than the United States. *Id.* at 3. However, that is true for all countries other than the United States but Europe still had more than 80% of global use of biosimilars and thus is still an important example of how to incentivize biosimilar use. *Id.*

375. See, e.g., Moorkens et al., *supra* note 67, at 5, 8–9; Rémuzat, *Supply Side*, *supra* note 67, at 6–7 (noting financial penalties for doctors who do not meet quotas or alternatively financial rewards for those who meet targets); Thomas Bo Jensen, Seoyoung C. Kim, Espen Jimenez-Solem, Dorthe Bartels, Hanne Rolighed Christensen, & Jon Trærup Anderson, *Shift from Adalimumab Originator to Biosimilars in Denmark*, 180 JAMA INTERNAL MED. 902, 902–03 (2020) (noting that Denmark bought biosimilars of brand biologic Humira through national tenders and achieved price cuts of one-fifth); see also Alan Cassels, *Why Biosimilars Should be Interchangeable*, PHARM. J. (Jan. 9, 2017), <https://pharmaceutical-journal.com/article/opinion/why-biosimilars-should-be-interchangeable-with-biologics> (noting that drug company lobbying is more successful in the U.S. than in Europe and thus operates to restrain biosimilar use).

376. Cécile Rémuzat, Julie Dorey, Olivier Cristeau, Dan Ionescu, Gueric Radière, & Mondher Toumi, *Key Drivers for Market Penetration of Biosimilars in Europe*, 5 J. MKT. ACCESS & HEALTH POL'Y 1, 7–9 (2017).

377. Rémuzat, *Supply Side*, *supra* note 67, at 9.

378. See GREENE, *supra* note 356, at 152 (discussing formularies that promote generics with lower co-pays).

379. Rémuzat et al., *supra* note 379, at 3; see also Frank et al., Working Paper 2021, *supra* note 97, at 18–19 (noting that in the United States, sometimes the originator will reduce its price with biosimilar entry).

A different type of financial incentive targets patients and doctors. For example, at one UK hospital, all stakeholders, including patients who were to be treated with a biosimilar for inflammatory bowel disease, were involved in designing a successful switching program to biosimilar infliximab, which has been the basis for broader policy recommendations for benefit sharing.<sup>380</sup> The program involved patient education on biosimilars and investing savings gained from lower cost biosimilars in new patient services, such as dietician support and specialist nurses.<sup>381</sup> All patients treated at the hospital were offered the opportunity to switch and 99% of patients accepted.<sup>382</sup> The researchers concluded this was likely due to improved patient understanding of the science and regulatory process, as well as benefits in terms of new services.<sup>383</sup> As will be discussed, Medicare could be modified to promote a semblance of cost sharing for doctors and patients that could be expected to have positive results based on this example.<sup>384</sup>

A recurring theme in studies of successful biosimilar use is the importance of education. Even in countries with financial incentives favoring biosimilars, studies note that it is important to combat limited knowledge of biosimilars among doctors and patients.<sup>385</sup> One study noted prescribers' "positive attitude and trust in biosimilar medicines should be the priority."<sup>386</sup> These comments would equally apply to the United States given that a 2020 study of U.S. patients indicated more than 80% trust doctors a great deal to make the right decisions and 70% would accept a biosimilar if their doctor prescribed it.<sup>387</sup> Although the importance of education has been repeatedly noted and even underscored by a 2021 federal law (mandating the Secretary of Health and Human Services to provide web-based

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380. IMPROVING HEALTHCARE DELIVERY IN HOSPITALS BY OPTIMIZED UTILIZATION OF MEDICINES: A STUDY INTO 8 EUROPEAN COUNTRIES, COMMISSIONED BY MEDICINES FOR EUROPE, KPMG 119 (2019); ARAD ET AL., *supra* note 293, at 9 (noting cost sharing not only in the UK, but also in France and Germany); James C. Robinson & Quentin Jarrion, *Competition from Biosimilars Drives Price Reductions for Biologics in the French Single Payer Health System*, 40 HEALTH AFFS. 1190, 1196 (2021) (noting that although France has a single payer health-care system, permitting hospitals to retain half of savings from biosimilars encouraged their use); *see also* Liese Barbier, Steven Simoens, Arnold G. Vulto, & Isabelle Huys, *European Stakeholder Learnings Regarding Biosimilars: Part II—Improving Biosimilar Use in Clinical Practice*, 34 BIODRUGS 797, 805 (2020) (noting surveyed doctors, nurses, and some regulators believed financial incentive would help incentivize switching to biosimilar especially since a switch requires significant planning and time).

381. Violeta Razanskaite, Marion Bettey, Louise Downey, Julia Wright, James Callaghan, Miles Rush, Simon Whiteoak, Sarah Ker, Kim Perry, Caron Underhill, Eren Efrem, Iftikar Ahmed, & Fraser Cummings, *Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme*, 11 J. CROHNS & COLITIS 690, 691 (2017).

382. *Id.* at 692.

383. *Id.* at 695.

384. *See infra* Section IV.B.3.b. (discussing Medicare cost sharing).

385. *See, e.g.*, Moorkens et al., *supra* note 67, at 10; Jorge Mestre-Ferrandiz, Adrian Towse, & Mikel Berdud, *Biosimilars: How Can Payers Get Long-Term Savings?*, 34 PHARMACOECONOMICS 609, 613 (2016); Laurence Greene, Rubina M. Singh, Mary Jo Carden, Caroline O. Pardo, & Gary R. Lichtenstein, *Strategies for Overcoming Barriers to Adopting Biosimilars and Achieving Goals of the Biologics Price Competition and Innovation Act: A Survey of Managed Care and Specialty Pharmacy Professionals*, 25 J. MANAGED CARE & SPECIALTY PHARMACY 904, 908–09 (2019).

386. Rémuzat, *Supply Side*, *supra* note 67, at 10.

387. NORC, *supra* note 13, at 4.

educational materials for doctors and patients), exactly what that education includes to minimize existing biases is an important yet nuanced issue that this Article aims to shed light on.<sup>388</sup>

## ii. Models of Effective Biosimilar Use in the United States

The best example of how biosimilar usage can be promoted in the United States comes from Kaiser Permanente. Although Kaiser is an unusual integrated health-care company that is a payor as well as employer of doctors, its strong biosimilar usage compared to the rest of the U.S. market makes it a case study for consideration.<sup>389</sup> There are a couple factors that may contribute to its successful biosimilar use. First, doctors do not have a financial incentive to use the originator biologic because doctors are not paid for services such as providing infusions,<sup>390</sup> and Kaiser also does not accept any rebates from originator biologic companies.<sup>391</sup> So, contrary to most U.S. insurers, there is no financial incentive for Kaiser doctors to choose originator biologics.<sup>392</sup> In addition, Kaiser incorporates doctor input in deciding what drugs to cover and only covers one biosimilar per drug class to strongly promote use of that biosimilar. Moreover, Kaiser is not swayed by unfounded safety concerns and instead evaluates its own patient use. Once Kaiser decides that biosimilars are safe and effective, it educates doctors,<sup>393</sup> utilizing a team of research pharmacists to disseminate information and answer questions.<sup>394</sup>

Although an integrated approach that includes both financial incentives and education is ideal, there is some evidence that improved education alone can result in successful switching to biosimilars. In the United

388. Advancing Education on Biosimilars Act of 2021, Pub. L. No. 117-8, 135 Stat. 254.

389. See, e.g., Sameer Awsare, Anthony Barrueta, Amy Gutierrez, & Polly F. Webster, *The Case for Letting Biosimilars Compete*, HEALTH AFFS. (Dec. 19, 2019), <https://www.healthaffairs.org/doi/10.1377/forefront.20191212.286621/full/> (noting Kaiser use of Zarxio is 95% compared to 31.7% for the rest of the market and use of biosimilar Inflectra is 80% versus under 4% for rest of market); In addition, Kaiser has had rapid adoption of biosimilars that included 97% biosimilar adoption of an oncology drug within a mere month of launch. Stanton Mehr, *How Did Kaiser Permanente Reach 95%+ Utilization of Biosimilar Herceptin and Avastin so Quickly?*, BIOSIMILAR REV. & REP. (Nov. 7, 2019), <https://biosimilarsr.com/2019/11/07/how-did-kaiser-permanente-reach-95-utilization-of-biosimilar-herceptin-and-avastin-so-quickly/>.

390. E.g., Awsare et al., *supra* note 392.

391. See Mehr, *supra* note 392. Rebates by brand companies have been noted as a problem in incentivizing payors to use the brand and financially benefiting, but not passing on their cost savings to consumers. Shepherd, *supra* note 309, at 376; Katie Thomas, *Meet the Rebate, the New Villain of High Drug Prices*, N.Y. TIMES (July 27, 2018), <https://www.nytimes.com/2018/07/27/health/rebates-high-drug-prices-trump.html>.

392. See Richard Brasington & Vibeke Strand, *New Treatments in Rheumatology: Biosimilars*, 6 CURRENT TREATMENT OPS. RHEUMATOLOGY 325, 330, 333 (2020) (explaining that in the United States there is a financial incentive to use brand biologics based on reimbursements and rebates, but Kaiser's refusal to accept rebates limits the financial incentive to use brand biologics and favors the use of biosimilars).

393. Mehr, *supra* note 392.

394. Letter from Kaiser Permanente to Alex. M. Azar, U.S. Dep't Health & Human Servs., Feb. 12, 2019, at 2. Kaiser also has a registry to address concerns for patients switched to a biosimilar, although there does not seem to be any evidence of difference regarding safety and efficacy for patients switched to the biosimilar. Brasington & Strand, *supra* note 392, at 333.

States, 97% of patients at an academic medical center whose insurance permitted coverage of a biosimilar were successfully switched from Remicade to a biosimilar to treat inflammatory bowel disease.<sup>395</sup> The patients experienced no significant clinical differences, yet recognized a total cost savings of \$500,000 per year for 150 patients.<sup>396</sup> This required involvement of key stakeholders to approve a formulary change to prefer the biosimilar, as well as education of doctors that included clinical evidence from the United States and the EU, and education of individual patients.<sup>397</sup> In addition to educating patients about the appropriateness of biosimilars, patients were told that because biosimilars cost less for insurers to cover than originator biologics, use of biosimilars over time could lower insurance premiums and out-of-pocket costs.<sup>398</sup>

### *B. Promoting Biosimilar Use in the United States Despite Biases*

Because this Article has demonstrated that the hesitancy to use biosimilars is likely due to an illogical bias, this Section focuses on modifying existing structures to nudge individuals to adopt biosimilars despite this bias. As discussed in the last Section, structural changes can result in desired behavior. Accordingly, this Section proposes changes to structural impediments, including existing laws that are perpetuating the bias, in conjunction with appropriate education and incentives.

This Section begins by suggesting reversal of the most significant structural changes, including unique aspects of U.S. law that perpetuate bias by suggesting skepticism against biosimilars. Even if this is not possible immediately, a critical component to minimize bias against biosimilars and increase usage is appropriate education of doctors to reduce illogical biases against biosimilars that in turn can help to reduce bias in patients. Lastly, this Section recommends financial incentives to promote biosimilar usage. Although financial incentives have had a major impact with promoting generic use, this is considered last because the nocebo effects are likely stronger with biologics than with generics. Financial incentives alone will not necessarily have desired outcomes without educating doctors on the existence of nocebo effects and how to reduce them.

#### 1. Removing Structural Biases and Barriers in Existing Laws

Two unusual structural impediments to biosimilar use lie with unique U.S. regulatory approaches to biosimilars. First, the United States has taken a different approach from all other nations by creating a separate designation to permit biosimilars to be automatically substituted by

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395. Shuba Bhat, Sarah Altajar, Divya Shankar, Toni Zahorian, Regine Robert, Taha Qazi, Bhavesh Shah, & Francis A. Farraye, *Process and Clinical Outcomes of a Biosimilar Adoption Program with Infliximab-Dyyb*, 26 J. MANAGED CARE & SPECIALTY PHARMACY 410, 413–14 (2020).

396. *Id.*

397. *Id.* at 411–13.

398. *Id.* at 412.

pharmacists.<sup>399</sup> Second, the United States also requires that biosimilars have a different nonproprietary name than their corollary biologic, which may result in an improper misperception of a significant difference because generic versions of traditional drugs lack such distinctions.<sup>400</sup> Given that European countries have broader acceptance and adoption of biosimilars and do not have either of these requirements, removing these impediments seems like a helpful first step.<sup>401</sup> This Section acknowledges that changing the status quo is challenging, especially because pharmaceutical manufacturers are a key stakeholder in negotiating the current laws and have shown substantial lobbying power in creating restrictive state laws limiting substitution.<sup>402</sup> Nonetheless, understanding what would be ideal can still be valuable in recognizing that the current structure is promoting bias and could be harnessed in education efforts as discussed in the next Section.

a. Addressing Interchangeability

It is important to ensure the interchangeability designation functions as it was originally intended, to promote biosimilar use, rather than propagate misperceptions that any biosimilar that is not interchangeable is suspect. Although there are few countries that have laws to promote pharmacy substitution of lower cost biosimilars, most other countries have more effective mechanisms to promote biosimilar use.<sup>403</sup> For example, some countries impose quotas on doctors to promote biosimilar and generic use.<sup>404</sup> Other countries may require biosimilar use because the national health-care system elected to purchase the cheaper biosimilar or at least may encourage biosimilar use through national mandates that require that biosimilars cost less.<sup>405</sup> Given these other levers, pharmacy substitution may not be as important in other countries, but it is important in the United States where these levers do not and are unlikely to exist.<sup>406</sup>

There are two possible ways to address systemic barriers to use of interchangeable biosimilars, one of which would be faster although more

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399. See *supra* text accompanying note 66 (discussing interchangeability requirement in U.S. law being unique).

400. See *supra* text accompanying note 219 (discussing how the United States has different nonproprietary names).

401. WAXMAN ET AL., *supra* note 294, at 16 (noting that naming and labeling rules may make doctors uncertain about biosimilars).

402. See Macfarlane, *supra* note 230, at 66–67 (discussing corporate lobbying to enact state anti-substitution laws for biosimilars).

403. See *supra* notes 377–91 and accompanying text (discussing efforts in other countries to promote biosimilar use).

404. E.g., Rémuzat, *Supply Side*, *supra* note 67, at 6–7 (noting quotas in eight European countries); Moorkens et al., *supra* note 67, at 8–9, 12 (discussing strategies aimed at doctors).

405. E.g., Brasington & Strand, *supra* note 392, at 333 (noting Denmark required patients to switch to biosimilars in 2016 as a cost-saving measure); Moorkens et al., *supra* note 67, at 5–8 (providing overview of pricing issues); see also ARAD ET AL., *supra* note 293, at 11 (noting that countries are moving away from a contract with a single biosimilar manufacturer to promote competition among biosimilar suppliers).

406. E.g., ARAD ET AL., *supra* note 293, at 8 (noting differences between U.S. and European systems concerning degree of government involvement in pricing of drugs and price negotiation).



challenging to implement. The ideal way to dismantle current barriers to biosimilar substitution is to create a federal mechanism for permitting substitution of biosimilars that would supersede state laws. This could include rules that would promote rather than limit usage, such as barring patients from objecting to substitution.<sup>407</sup> A federal system for substitution would not replace the existing scheme for evaluating what is interchangeable at the pharmacy level. However, importantly, it would avoid the current hurdles in state laws that originator biologic companies have successfully lobbied for states to enact. Such companies are likely to object to anything that would dismantle laws they created with substantial and expensive lobbying.<sup>408</sup> Accordingly, the second approach is a piecemeal one. As the history of generic state substitution laws shows, it is also possible to change laws over time on a piecemeal basis.<sup>409</sup> Notably, that history indicates that a strong coalition of competing forces, along with financial imperative, may be necessary to prompt change.<sup>410</sup> A financial imperative should be obvious given that biologics comprise a disproportionate part of expenses while constituting a minority of drugs—especially because more biologics are likely to enter the market and further increase financial strains.<sup>411</sup> Perhaps with appropriate education of doctors and advocacy from consumer groups with aligned interests, state laws to better promote substitution of interchangeable biosimilars would be possible.

#### b. Addressing Suffixes for Biosimilars

Whereas the interchangeability designation is difficult to change, it should be easier to modify existing U.S. regulations concerning distinct suffixes for the nonproprietary names of biosimilars given that there is no need for congressional action and no robust reason for the rule. The origin of distinct names is tied to industry lobbying asserting that distinct naming ensure safety.<sup>412</sup> FDA guidance similarly alleges suffixes could improve pharmacovigilance.<sup>413</sup> However, this is contrary to real-life data. The EU, for example, does not use suffixes and has not had any trouble with

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407. *E.g.*, Daniel Kadin, Note, *Taking Biosimilars to the Next Level: Why Federalizing the Substitution of Biosimilars Promotes Innovation, Competition, and Patient Safety*, 45 SW. L. REV. 405, 422–27 (2015).

408. *E.g.*, Macfarlane, *supra* note 230, at 66–67 (noting company lobbying to create state legislation limiting biosimilar substitution); Andrew Pollack, *Biotech Firms, Billions at Risk, Lobby States to Limit Generics*, N.Y. TIMES (Jan. 28, 2013), <https://www.nytimes.com/2013/01/29/business/battle-in-states-on-generic-copies-of-biotech-drugs.html>.

409. *See supra* notes 358–65 and accompanying text (discussing history of U.S. structural changes to law and policy).

410. *See supra* notes 333–36 and accompanying text.

411. *E.g.*, *supra* notes 1–2 and accompanying text (noting that biologics constitutes 40% of drug costs although they are only about 2% of drugs used).

412. BIO, EBE, EFPIA, EUROPABIO, IFPMA, & PHRMA, POLICY POSITION ON NAMING OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS 3–4 (Oct. 31, 2006); Mendila, *supra* note 248 (Genentech argued “distinct” names are essential to avoid unintended substitution even though that does not seem to be a problem with generics that share the same name).

413. 2017 DRAFT NAMING GUIDANCE, *supra* note 240, at 4–6; *see also* 2019 DRAFT NAMING GUIDANCE, *supra* note 236, at 5–6 (revising guidance to not require suffixes for biologics approved without an FDA suffix).

tracking biosimilars by using brand names in conjunction with other identifiers, such as batch numbers.<sup>414</sup> Moreover, despite the FDA claim that unique suffixes help with tracking adverse reactions, less than 1% of reported adverse reactions actually use the suffix; rather, virtually all reports are based on the brand name, as is the case in Europe.<sup>415</sup> The FDA seemed to see the fallacy of different names when it briefly suggested suffixes for all biologics, including retroactively applying them to originator biologics.<sup>416</sup> However, current FDA guidance now reflects brand manufacturer claims that retroactive suffixes cause undue burden.<sup>417</sup> This argument is not compelling. Even if there is a financial cost to changing suffixes, the overall economic cost of bias against biosimilars should be given greater weight. The annual savings of \$2–\$7 billion resulting from increased use of biosimilars would make the onetime cost of changing product names insignificant.<sup>418</sup>

Jettisoning use of suffixes for all biologics is ideal. If this is not possible, having suffixes associated with the manufacturer would better parallel the system with generics where the generic has the same nonproprietary name, but pharmacists can distinguish between different manufacturers. Indeed, pharmacists currently have trouble associating the random suffixes that the FDA requires with specific biosimilars, which is likely because the meaningless suffix makes it hard to remember.<sup>419</sup>

At a minimum, it is desirable for at least interchangeable biosimilars to share the same proprietary name, including the suffix.<sup>420</sup> The FDA only grants an interchangeable designation to a biosimilar that can be substituted by a pharmacist when it is supported by extensive data on the safety of multiple switches. Sharing the same name would underscore that such biosimilars can be substituted in the same manner as generics. Admittedly, this would require that a biosimilar's nonproprietary name change once the biosimilar is deemed interchangeable. The FDA asserts that it might cause unnecessary confusion if a biosimilar was later deemed interchangeable and needed a name change.<sup>421</sup> However, this ignores the fact that

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414. EUR. MEDS. AGENCY & EUR. COMM'N, *supra* note 66, at 25–26; Niels S. Vermeer, Thijs J. Giezen, Sofia Zastavnik, Elena Wolff-Holz, & Ana Hidalgo-Simon, *Identifiability of Biologics in Adverse Drug Reports Received from European Clinical Practice*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 962, 964, 967–68 (2018).

415. Stanton Mehr, *More from GRx+ Biosims on Four-Letter Suffixes and Biosimilar Interchangeability*, BIOSIMILARS REV. & REP. (Sept. 20, 2018), <https://biosimilarsrr.com/2018/09/20/more-from-grxbiosims-on-interchangeability/>.

416. 2017 DRAFT NAMING GUIDANCE, *supra* note 240, at 7.

417. 2019 DRAFT NAMING GUIDANCE, *supra* note 236, at 5–6; *see also* Stanton Mehr, *If Four Letter Suffixes Aren't Used in Biosimilar Tracking, What Use are They?*, BIOSIMILAR DEV. (Nov. 6, 2018), <https://www.biosimilardevelopment.com/doc/if-four-letter-suffixes-aren-t-used-in-biosimilar-tracking-what-use-are-they-000> (arguing that changing suffixes for currently marketed biologics would involve forty hours per product).

418. WINEGARDEN, *supra* note 102, at 5.

419. Stephen Barlas, *FDA Pleases No One with Final Guidance on Naming of Biologics and Biosimilars*, 42 PHARMACY & THERAPEUTICS 222, 222 (2017).

420. The FDA did contemplate this as a possible option. *See* FDA, *Nonproprietary Naming of Biological Products: Draft Guidance for Industry*, 80 Fed. Reg. 52,296 (Aug. 2015).

421. 2019 DRAFT NAMING GUIDANCE, *supra* note 236, at 6.

distinct nonproprietary names already cause confusion and bias against biosimilars.<sup>422</sup> Moreover, a name change for an interchangeable biosimilar would serve an important signaling function as to its changed status.

## 2. Enlightened Education in View of Bias and Nocebo Effect

Even if existing U.S. structural barriers to biosimilar use are not eliminated, biosimilars can nonetheless be promoted with appropriate education that is cognizant of bias against biosimilars. Notably, although many have suggested that education of doctors and patients is important, the type of education is critical.<sup>423</sup> As discussed earlier, accurate facts do not necessarily change views because cognitive biases can distort how facts are perceived.<sup>424</sup> Moreover, biosimilar bias adds an additional layer of complication. Considering that biosimilars treat more serious conditions, patients who are switched to a biosimilar could likely experience a nocebo effect.<sup>425</sup> So, patient education must be carefully tailored to reduce this effect.

Doctors are the starting place for improving knowledge about biosimilars to reduce illogical bias because they can influence patients and payors. Many patients are willing to switch from a brand to biosimilar if advised by a physician.<sup>426</sup> Even payors are sensitive to doctor preferences; some have suggested that insurers thus far have been resistant to preferring biosimilars because of strong doctor aversion to switching stable patients.<sup>427</sup> In addition, once doctors are familiar with biosimilars, they may adopt subsequent ones more easily.<sup>428</sup>

The first thing to educate doctors on is that all biosimilars—even if not designated as interchangeable—are safe and effective. It may be helpful to educate doctors on the long history of biosimilar use in Europe as well as the rigorous clinical trials establishing safety and efficacy. Moreover, doctors should be informed that the interchangeable designation is a unique U.S. designation to promote greater use of biosimilars rather than a signal of a problem, and that a similar designation does not exist in other countries because they have other levers to promote biosimilar use inapplicable to the United States, such as government purchasing of lower cost

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422. Socal et al., *supra* note 271, at 278; *see also* Kolbe et al., *supra* note 166, at 368 (noting that 46% of doctors said that suffixes make prescribing confusing).

423. *See generally supra* notes 385–88 and accompanying text (discussing need for education).

424. *See supra* notes 112–15 and accompanying text.

425. *See, e.g., supra* notes 197–206 and accompanying text (discussing likely nocebo effect with biosimilars); Wolfe & Michaud, *supra* note 140, at 2135 (finding that RA patients not entirely satisfied with existing therapy are reluctant to try new treatment for fear that it could be worse).

426. Scherlinger et al., *supra* note 197, at 930 (noting that 70% of patients willing to switch to a biosimilar for rheumatic disease involved a situation where the doctor had a good opinion of biosimilars and patient trust in doctor opinion was considered important whereas only 30% were persuaded by cost).

427. Hakim & Ross, *supra* note 230, at 2164.

428. BIOSIMILARS FORUM, *supra* note 81, at 11.

biosimilars for all. Essentially, education should seek to counter misinformation about the importance of the interchangeability designation.

Another important component is to educate doctors that it is safe to switch patients currently on an originator biologic to a biosimilar. Studies have repeatedly noted that it is impossible to substantially reduce overall costs if only new patients, who are the minority of total patients, are switched to biosimilars; existing patients must also be switched.<sup>429</sup> However, current bias against biosimilars coupled with advertisements that repeatedly caution against “non-medical switching” can promote the cognitive bias of loss aversion, which creates an unnecessary hesitance to change medication.<sup>430</sup> Indeed, one study revealed that including the term non-medical switching in a survey question changed doctor willingness to switch patients.<sup>431</sup> This is not surprising because the term suggests that a biosimilar would be used when it is not medically appropriate, as opposed to using a biosimilar that is just as medically appropriate but more cost effective than the originator biologic.<sup>432</sup> In addition, although marketing and materials from some patient advocate groups emphasize a list of problems that could result from switching to a biosimilar, those same problems could happen without any switch because each batch of biologics, even if from the same manufacturer, is not identical.<sup>433</sup> Moreover, there is both empirical evidence and real-life data from other countries showing that switching is safe, which has persuaded some countries to mandate switching to biosimilars to maximize access to expensive biologics.<sup>434</sup> This fact needs to be impressed on doctors, along with recent guidance from many doctor groups in Europe promoting greater biosimilar use even for patients who are currently stable on a biologic. In addition, perhaps a different term should be used—such as “safe switching”—to promote the idea that switching is safe, or at least neutrally referring to it simply as “switching,” which some academic articles do.<sup>435</sup>

A critical component that has not been acknowledged by the FDA or most commentators is that doctors need to be educated on the nocebo effect to minimize it.<sup>436</sup> Most fundamentally, doctors need to know that this

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429. *E.g.*, Hakim & Ross, *supra* note 230, at 2164. This is likely due to the fact that most biologics do not cure diseases and rather are long-term maintenance drugs, such that existing patients make up a big part of biologic use.

430. *See supra* notes 134–39 and accompanying text (discussing loss aversion).

431. INDUS. STANDARD RSCH., *supra* note 288 and accompanying text.

432. *E.g.*, Anna Rose Welch, *Amgen, Sandoz Biosimilar FDA AdComs: 5 Takeaways*, BIOSIMILAR DEV. (July 18, 2016), <https://www.biosimilardevelopment.com/doc/amgen-sandoz-biosimilar-fda-adcoms-takeaways-0001> (noting that the term “non-medical switching” causes unnecessary concern and confusion).

433. Rahman Kabir et al., *supra* note 34 (noting that different batches of originator biologics are also not identical).

434. *E.g.*, Davio, *supra* note 280; Jeremias, *supra* note 280.

435. *See generally* Kurki et al., *supra* note 66, at 88.

436. *See* Ferdinando D’Amico, Lieven Pouillon, Marjorie Argollo, Ailsa Hart, Gionata Fiorino, Elena Vegni, Simona Radice, Daniela Gilardi, Maria Fazio, Salvo Leone, Stefanos Bonovas, Fernando Magro, Silvio Danese, & Laurent Peyrin-Biroulet, *Multidisciplinary Management of the Nocebo Effect*

phenomenon takes place and how doctor-patient communications, including nonverbal gestures, can prompt a nocebo effect. Importantly, even just one occasion of negative information can have long-lasting effects in terms of nocebo effects.<sup>437</sup> Of course, informing doctors about the nocebo effect and how to eliminate it will only be effective if doctors do not have a bias against biosimilars themselves.<sup>438</sup> Even assuming no bias, doctors should still be informed of specific strategies that can help generally reduce the nocebo effect, and specifically reduce the nocebo effect with biosimilars.<sup>439</sup>

How information is disclosed or not disclosed to patients can have an important impact on perceptions and subsequent nocebo effects. One Dutch study indicated that improved communication, including clearly informing patients about the reason for a switch to a biosimilar, together with “soft skills” such as training to address patient concerns and openly discussing possible nocebo effects, resulted in higher patient acceptance and persistence.<sup>440</sup> Beyond the nascent biosimilar context, there is evidence showing that negative framing may prompt nocebo effect<sup>441</sup> whereas positive framing can have positive effects. A balanced approach focuses on a positive framing rather than just listing the adverse effects.<sup>442</sup> Positive framing would focus on similarities in safety and efficacy rather than simply lower cost; this is important because patients sometimes improperly assume lower costs are associated with inferior products.<sup>443</sup>

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in *Biosimilar-Treated IBD Patients: Results of a Workshop from the NOCE-BIO Consensus Group*, 52 DIGESTIVE & LIVER DISEASE 138, 140 (2020) (noting that patient–health-care-provider relationship is a key driver in accepting biosimilars and limiting the risk of nocebo effect).

437. Rea Rodriguez-Raecke, Beril Doganci, Markus Breimhorst, Anne Stankewitz, Christian Büchel, Frank Birklein, & Arne May, *Insular Cortex Activity is Associated with Effects of Negative Expectation on Nociceptive Long-Term Habituation*, 30 J. NEUROSCIENCE 11363, 11366 (2010).

438. See *supra* notes 14–15 and accompanying text.

439. Greene et al., *supra* note 388, at 905 tbl.1. These are generally applicable strategies although those inclined to nocebo effects may share some characteristics. See Gasteiger et al., *supra* note 206, at 169 (finding that women that engage in more information-seeking behavior have more negative perceptions towards generics).

440. L. Tweehuysen, V.J.B. Huiskes, B.J.F. van den Bemt, F.H.J. van den Hoogan, & A.A. den Broeder, *Higher Acceptance and Persistence Rates After Biosimilar Transitioning in Patients with Rheumatic Disease After Employing an Enhanced Communication Strategy*, 17 ANNALS RHEUMATIC DISEASE 557, 557 (2017) (the improved communication included first informing patients by letter and then contacting by phone to see if they agreed, together with enhanced communication after the transition that explained that the transition would result in lower costs and fewer injection site reactions).

441. Ted J. Kaptchuk, William B. Stason, Roger B. Davis, Anna T. R. Legedza, Rosa N. Schnyer, Catherine E. Kerr, David A. Stone, Bong Hyun Nam, Irving Kirsch, & Rose H. Goldman, *Sham Device v. Inert Pill: Randomised Controlled Trial of Two Placebo Treatments*, 332 BRIT. MED. J. 1, 5–6 (2006) (subjects told of possible adverse effects experienced them even when given sham treatments); see also Luana Colloca, Leonardo Lopiano, Michele Lanotte, & Fabrizio Benedetti, *Overt Versus Covert Treatment for Pain, Anxiety, and Parkinsons*, 3 LANCET NEUROLOGY 679, 681 (2004) (telling patients when an infusion of morphine for postoperative pain would be interrupted resulted in more pain than patients who knew the infusion would eventually stop, but not the exact time).

442. Colloca & Finnis, *supra* note 338, at 568; Yannick Vandenplas, Steven Simoens, Philippe Van Wilder, Arnold G. Vulto, & Isabelle Huys, *Informing Patients About Biosimilar Medicines: The Role of European Patient Associations*, 14 PHARMS. 1, 6 (2021).

443. D’Amico et al., *supra* note 436, at 140–41; Frantzen et al., *supra* note 195, at 495 (noting that safety and efficacy data was the best incentive to convert patients to biosimilars and that doctors are the most persuasive source of information).

Indeed, one study found those in a positive framing group were more than two times more likely to switch to a biosimilar and were more likely to believe that the biosimilar would be effective.<sup>444</sup> In addition, educating patients on the fact that the differences between a biologic and a biosimilar are similar to those between different batches of originator biologics is also suggested as helpful to promoting patient acceptance.<sup>445</sup> Moreover, providing education both orally and in writing is recommended.<sup>446</sup> All of these considerations are particularly important for switching stable patients to a biosimilar to combat rampant negative messaging, the loss aversion cognitive bias, and the nocebo effect.<sup>447</sup>

In terms of how to educate doctors, a broad effort is important. To address the availability bias that has been promoting originator biologic views, the education effort must be substantial enough to make it equally available. This would require far more than just FDA guidance, which is not as available as advertisements. However, the same techniques that work to promote brand name drugs can be used to properly educate doctors. For example, studies have shown success with so-called academic detailing of generic drugs where doctors are visited and provided information on generics to counteract advertising of brand drugs.<sup>448</sup> In addition, just as European groups of doctors in particular areas have adopted consensus statements promoting use of biosimilars, so too U.S. doctors could establish similar statements and—before those statements take effect—promote existing statements from their European peers with more experience.<sup>449</sup>

In addition, just as a coalition of interest groups helped to promote generic usage, incorporating groups beyond the FDA interested in promoting biosimilar use would also be valuable. It would be ideal if patient advocacy groups could provide similar education. Not only could patient advocacy groups make information promoting biosimilars more available to counteract marketing from brand biosimilars, but these groups are often especially trusted by patients.<sup>450</sup> Studies focused on debunking

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444. Chiara Gasteiger, Annie S. K. Jones, Maria Kleinstäuber, Maria Lobo, Rob Horne, Nicola Dalbeth, & Keith J. Petrie, *Effect of Message Framing on Patients' Perceptions and Willingness to Change to a Biosimilar in a Hypothetical Drug Switch*, 72 *ARTHRITIS CARE & RES.* 1323, 1327 (2020).

445. Scherlinger et al., *supra* note 197, at 930. However, the level of detail to provide is difficult to determine because more information might prompt patients to assume that there is a problem. *E.g.*, Barbier et al., *supra* note 181, at 734 (noting no consensus on this issue among doctors and nurses).

446. Scherlinger et al., *supra* note 197, at 931.

447. This is particularly important given a recent study indicating that doctor and patient perceptions about whether adequate information was provided regarding switching to a biosimilar differed, with less than half of patients believing their cancer would be treated effectively with a biosimilar versus 79% of oncologists, and also the majority of oncologists believing the switch was a minor change, but only 37% of patients seeing it as minor. *E.g.*, Tony Hagen, *Patient-Provider Surveys Elucidate Biosimilar Switching Process in Oncology*, *CTR. FOR BIOSIMILARS* (Dec. 13, 2021), <https://www.centerforbiosimilars.com/view/patient-provider-surveys-elucidate-biosimilar-switching-process-in-oncology>.

448. See Jerry Avorn, *Academic Detailing: "Marketing" the Best Evidence to Clinicians*, 317 *J. AM. MED. ASS'N* 361, 361 (2017).

449. See generally *MEDICINES FOR EUROPE*, *supra* note 2268, *passim*.

450. *E.g.*, Vandenplas et al., *supra* note 442, at 10.

misinformation indicate more success when information is presented in a way that aligns with personal beliefs or partisan identities.<sup>451</sup> Patients may feel such groups represent their interests and thus, be more amenable to their positions like partisan identity.<sup>452</sup> Admittedly, it may be challenging to persuade patient advocacy groups to promote biosimilars because many of them are aligned with originator biologic interests.<sup>453</sup> Even if patient advocacy groups are not readily amenable, there could be other entities with an interest in promoting biosimilars such as AARP, which also helped to promote generic use.<sup>454</sup>

Another mechanism to promote availability of positive messages concerning biosimilar use would be to simultaneously reduce availability of inaccurate messages from originator biologic manufacturers. Beyond the FDA taking more direct action to immediately correct messages, additional steps could be taken to further eliminate some current structural oddities that incentivize corporate mismarketing. For example, Congress could remove tax deductions that currently apply to direct-to-consumer advertising and instead, apply taxes on “spending on direct-to-consumer broadcast advertising.”<sup>455</sup>

### 3. Financial Incentives

Last, but not least, financial incentives should promote biosimilar use in a manner similar to what has worked with generics, rather than the current situation that promotes the originator.<sup>456</sup> Of course, how to do so is much more complex than with generic drugs given that biologics are primarily provided by doctors rather than pharmacists. However, there are different and complementary ways to realign incentives that include disincentivizing rebates that favor the originator biologic and financial incentives to doctors and patients to use biosimilars.

#### a. Incentivize Biosimilar Coverage

One of the most obvious steps is to prevent payors from requiring patients to fail first on the originator biologic before giving access to a

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451. *E.g.*, Lewandowsky et al., *supra* note 15, at 118.

452. *See, e.g.*, Vandenplas et al., *supra* note 442, at 10.

453. *See supra* notes 241–42 and accompanying text; *see also supra* Section III.B.2 (noting that companies and patient advocacy groups both discourage switching to biosimilars).

454. *See supra* note 362 and accompanying text.

455. WAXMAN ET AL., *supra* note 294, at 19.

456. Although other countries have mandated biosimilar use, this is inconsistent with U.S. history. *See supra* Section III.A. Moreover, mandatory use could increase overall health-care costs, possibly due to a nocebo effect. However, Denmark has successfully required patients switch to biosimilars without an increase in health-care service costs. *See, e.g.*, Bente Glintborg, Rikke Ibsen, Rebecca Elisabeth Qwist Bilbo, Merete Lund Hetland, & Jakob Kjellberg, *Does a Mandatory Non-Medical Switch from Originator to Biosimilar Etanercept Lead to Increase in Healthcare Use and Costs? A Danish Register-Based Study of Patients with Inflammatory Arthritis*, RMD OPEN 1, 6, 8 (2019); Bente Glintborg, Jan Sørensen, & Merete Lund Hetland, *Does a Mandatory Non-Medical Switch from Originator to Biosimilar Infliximab Lead to Increased Use of Outpatient Healthcare Resources? A Register-Based Study in Patients with Inflammatory Arthritis*, RMD OPEN 1, 4 (2018).

biosimilar.<sup>457</sup> Just as generic drug use has been promoted with tiered formularies that provide substantially reduced or zero co-pays for generics, a similar framework would be helpful to promote use of biosimilars.<sup>458</sup> At a minimum, it would be desirable to bar preference for originator biologics in formularies. While contrary to most existing practices in the United States, one proposed state bill aims to do this.<sup>459</sup> In addition, some insurers may already be doing so with use of biosimilars for patients new to expensive oncology treatments.<sup>460</sup>

There is also a need to address the rebate trap that results in insurers preferring brands to increase their profits. Addressing rebates is complex. A Trump Administration rule, currently on hold,<sup>461</sup> proposed to bar rebates for Medicare drugs under Part D that covers some common biologics, such as insulin.<sup>462</sup> Although barring rebates for Medicare might promote biosimilar use, some suggested that it would increase premiums because insurers allegedly provide lower premiums due to the rebates.<sup>463</sup> Although exploring the details of how to minimize rebate use without increasing Medicare premiums is beyond the scope of this Article, this Article agrees that anticompetitive rebates should be avoided.<sup>464</sup>

Given the diversity of private payors, starting with Medicare reform makes sense because private insurers often take cues concerning coverage from Medicare.<sup>465</sup> The need to amend Medicare to better align incentives is something that is already recognized by some policy makers as helpful,<sup>466</sup> indeed, Congress has already modified some Medicare benefits to promote biosimilars dispensed at pharmacies.<sup>467</sup> However, Medicare can and should also promote biosimilar administration in doctor offices, such as by covering biosimilars and their corollary originator biologic under the same billing code so that reimbursement is based on an average price that includes both and provides an incentive for true price competition.<sup>468</sup> In

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457. *E.g.*, AVALERE HEALTH, *supra* note 309, at 8.

458. *See supra* notes 375–76 and accompanying text (discussing tiered formularies incentivizing use of generics).

459. S. 990, 2021 Leg., 92d Sess. (Minn. 2021).

460. *See supra* note 307 and accompanying text.

461. Pharm. Care Mgmt. Ass'n v. U.S. Dept. Health & Human Servs., No. 21-95 (JDB), 2021 U.S. Dist. LEXIS 30884, at \*2 (D.D.C. Jan. 30, 2021).

462. 42 C.F.R. § 1001.952(h).

463. Jeff Lagasse, *Trump-Era Rebate Rule for Medicare Part D on Hold Until 2023*, HEALTHCARE FINANCE (Feb. 1, 2021), <https://www.healthcarefinancenews.com/news/biden-administration-puts-hold-trump-era-rebate-rule-medicare-part-d>.

464. For some specific suggestions to address anticompetitive practices, see WAXMAN ET AL., *supra* note 294, at 19.

465. *E.g.*, Yazdany, *supra* note 290, at 871.

466. *E.g.*, BRILL, *supra* note 6, at 6–7; ARAD ET AL., *supra* note 293, at 9.

467. Medicare benefits for biosimilars distributed at pharmacies have been modified to correct a prior situation where there was a discount for brand biologic manufacturer, but not biosimilars for the “gap phase” of Medicare Part 2. *See* Bipartisan Budget Act of 2018, Pub. L. No. 115–123, §§50323–25, 132 Stat. 64, 169.

468. *E.g.*, Benjamin N. Rome & Ameet Sarpatwari, *Promoting Biosimilar Competition by Revising Medicare Reimbursement Rules*, JAMA NETWORK OPEN, Nov. 15, 2021, at 1, 1 (explaining that this is the situation for traditional drugs and the result is direct price competition between brand name and generics that incentivizes doctors to purchase and administer the least expensive option).



addition, even without amendment of Medicare rules, it is possible to use different strategies through the Center for Medicare and Medicaid Innovation, which is designed to test innovative payment and service delivery models to reduce costs like the suggestions below or, alternatively, like the models that have worked for Kaiser and in Europe.<sup>469</sup>

#### b. Promoting Biosimilars Through Medicare Modification

Biosimilars could be promoted by modifying Part B of Medicare, which addresses the many biologics administered in health-care provider offices. There are currently proposals to modify the law.<sup>470</sup> Based on structural changes that have been effective globally, permitting a shared savings model for physicians whereby they receive a portion of the difference between the average sales price of the originator biologic and biosimilar—in addition to standard payments—could be effective. After all, shared savings have been effective in other countries.<sup>471</sup>

Medicare Part D could also be modified to promote biosimilars. Just as formulary tiers helped promote usage of generics, a formulary tier could financially prefer a biosimilar over a corresponding originator biologic.<sup>472</sup> In addition, requiring plans to add biosimilars to formularies as soon as they come on the market and removing step therapy requirements would also promote biosimilar use. Medicare could follow Kaiser's success in promoting biosimilars by only covering one biosimilar for every biologic, although this may require a change in the law because it currently requires two drugs per class with biosimilars not considered a different drug.<sup>473</sup> This would likely be most successful if coupled with a patient incentive, such as no patient co-pay for biosimilars.<sup>474</sup> Another possibility is to create a specialty tier for generics and biosimilars to promote cost sharing.

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469. *E.g.*, BRILL, *supra* note 6, at 5–9 (suggesting that this center engage in different Part B payments as well as promote shared savings); *see also* Kip Piper, *Medicare and Medicaid Demonstration Waivers*, PIPER REP. (Aug. 12, 2018), <https://piperreport.com/blog/2008/08/12/medicare-and-medicare-demonstration-waivers-primer/> (discussing possible waivers from usual Medicare and Medicaid rules).

470. S. 2543, 116th Cong. § 104 (2019) (recommending Medicare Part B provide biosimilars average sales price (ASP) plus 8% of the reference biologic price, instead of 6%). *But see* Chad Pettit, *The Case for Optimism in the U.S. Biosimilar Market*, BIOSIMILAR DEV. (July 28, 2020), <https://www.biosimilardevelopment.com/doc/the-case-for-optimism-in-the-u-s-biosimilar-market-0001> (arguing that such a change would provide inadequate incentive for biosimilar manufacturers to compete on price).

471. *See supra* notes 383–87 and accompanying text.

472. WAXMAN ET AL., *supra* note 294, at 15.

473. Memorandum from Amy K. Larrick, Acting Director, Medicare Drug Benefit and C & D Data Group, on Part D Requirements for Biosimilar Follow-On Biological Products to Part D Sponsors (Mar. 30, 2015) (available at [https://www.csscooperations.com/internet/cbts/mmp\\_cbt.nsf/HPMS-Memo\\_Biosimilars\\_5CR\\_033116.pdf](https://www.csscooperations.com/internet/cbts/mmp_cbt.nsf/HPMS-Memo_Biosimilars_5CR_033116.pdf)).

474. Memorandum from HarrisX on Topline Findings from Survey on Biosimilars and Medicare to Biosimilars Forum (Feb. 28, 2020) (available at <https://harrisx.com/wp-content/uploads/2020/03/Biosimilars-topline-poll-public-memo-VF.pdf>).

## CONCLUSION

The successful and safe use of more cost-effective biosimilars to treat more patients is an important, yet, thus far, elusive goal. This Article contributes to the literature by identifying the extent of existing bias against biosimilars, as well as the effect of U.S. law, policy, and private insurers on perpetuating bias and thus, barring broader U.S. adoption of biosimilars. Minimizing bias is difficult, and especially so because the current status quo favors originator biologics. Nonetheless, this Article provides multiple mechanisms to modify bias and change existing structures to effectively nudge desired action.