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## Suggestions for State Laws on Biosimilar Substitution

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## NOTE

# SUGGESTIONS FOR STATE LAWS ON BIOSIMILAR SUBSTITUTION

Gary M. Fox\*

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### ABSTRACT

*Biologic drugs offer major advancements over small-molecule drugs when it comes to treating serious diseases. Biosimilars, which mimic innovative biologic drugs, have the potential to further revolutionize the practice of medicine. States now have decades of experience regulating the substitution of generic, small-molecule drugs for their brand-name equivalents. But the complexities of biologic drugs and biosimilars force states to confront novel scientific and legal issues. Many states have begun tackling those issues by passing laws that regulate when pharmacists may substitute biosimilars for their corresponding biologic drugs. Other states have yet to do so. This Note surveys five provisions common throughout current legislation: interchangeability, indications to “Dispense as Written,” physician communication, patient notification, and recordkeeping. This Note goes on to argue that states without biosimilar substitution laws should embrace all of these provisions, except to the extent that notification provisions would allow patients to opt out of biosimilar substitution without a legitimate medical reason. If states can appropriately balance promoting biosimilars in the market while protecting patients’ safety, they can help more patients receive effective treatments while reducing spending on drugs.*

### INTRODUCTION

In 2015, healthcare spending in the United States increased at the fastest rate since the economic downturn in 2008.<sup>1</sup> The U.S. Department of Health

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\* J.D. Candidate, University of Michigan Law School; A.B. in Chemistry, Princeton University. I would like to thank Professor Rebecca Eisenberg for her comments on an earlier draft and her commitment to developing young scholars. Thanks also to Bethany Felder and Caleb Kennedy for helpful feedback. This Note was last revised at the start of 2018, but this area of the law is changing quickly. Any errors are mine alone.

1. Robert Pear, *U.S. Health Spending in 2015 Averaged Nearly \$10,000 Per Person*, N.Y. TIMES (Dec. 2, 2016), <http://www.nytimes.com/2016/12/02/us/politics/us-health-care-spending.html>.

and Human Services calculated the total annual cost at \$3.2 trillion—nearly 18% of the American economy.<sup>2</sup> In particular, spending on prescription drugs increased by 9% over the previous year to a total of nearly \$325 billion.<sup>3</sup> On average, the United States spends approximately twice as much on healthcare as other developed countries.<sup>4</sup> These numbers are alarming because increased healthcare costs potentially divert funds from other causes, like Social Security, education, and infrastructure.

Over the years, physicians, politicians, and professors have suggested ways to slow increasing healthcare costs. These commentators and policymakers aim to increase access to affordable medications (thereby lowering total healthcare costs) while still ensuring patient safety. One effective method for reducing the costs of small-molecule drugs is substituting generic versions for their corresponding brand-name counterparts.<sup>5</sup> In 2015 alone, generic, small-molecule drugs saved the U.S. healthcare system approximately \$232 billion.<sup>6</sup> Although physicians and patients may opt for generic drugs, substitutions largely occur because states have enacted laws requiring or permitting pharmacists to make them.<sup>7</sup> But not all state substitution laws have kept pace with recent advances in biotechnology.

It may be possible for the United States to decrease spending on healthcare by replacing brand-name biologic drugs with related biologics, known as biosimilars.<sup>8</sup> Congress created an abbreviated pathway for the U.S. Food and Drug Administration (FDA) to approve biosimilars as part of the Patient

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2. *Id.*

3. *Id.*

4. Ian Read, *All Americans Must Benefit from the Golden Age of Medicine*, FORBES (Nov. 29, 2016, 8:00 AM), <http://www.forbes.com/sites/sciencebiz/2016/11/29/all-americans-must-benefit-from-the-golden-age-of-medicine/#19f979452e0d>. Read notes, however, that spending on drugs in the United States more closely matches spending on drugs in other developed nations.

5. Small-molecule drugs are the drugs with which nearly everyone is familiar, as they comprise over 90% of available drugs. See *Small and Large Molecules*, BAYER, <http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/> (last visited Jan. 11, 2018). Small-molecule drugs “are synthesized in the classic way: by chemical reactions between different organic and/or inorganic compounds.” *Id.* The paradigmatic example is aspirin, which is easily formulated as a tablet. *Id.*

6. ASS’N FOR ACCESSIBLE MEDS., *Generic Drug Access & Savings in the U.S.* 39 (2017), <https://www.accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf>. But see Abigail Fagan, *Generic Drugs Offer \$73 Billion Savings*, SCIENCELINE (Nov. 14, 2016), <http://scienceline.org/2016/11/generic-drugs-offer-73-billion-savings/> (noting that the U.S. healthcare system could save an additional \$73 billion on other brand-to-generic substitutions); Melody Petersen, *Drug Costs Skyrocket for Many Older Americans, Despite Medicare Coverage*, L.A. TIMES (Nov. 23, 2016, 11:10 AM), <http://www.latimes.com/business/la-fi-medicare-drug-costs-20161123-story.html> (noting that costs for some generic drugs continue to increase).

7. See *infra* Part I.

8. Andrew Pollack, *Biotech Firms, Billions at Risk, Lobby States to Limit Generics*, N.Y. TIMES (Jan. 28, 2013), <http://www.nytimes.com/2013/01/29/business/battle-in-states-on-generic-copies-of-biotech-drugs.html>.

Protection and Affordable Care Act (ACA).<sup>9</sup> The FDA must approve biosimilars before they enter the market, but states retain the authority to determine when and how pharmacists substitute biosimilars for their corresponding brand-name biologic drugs (also known as “reference products”).<sup>10</sup> Although thirty-six states have already enacted laws governing how pharmacists may substitute biosimilars for prescribed biologic drugs, the remaining states have yet to do so.<sup>11</sup> Plus, all fifty states could still amend their laws before the first interchangeable biosimilar hits the market, i.e., when biosimilar substitutions are likely to become more common.<sup>12</sup>

This Note argues that current legislation for biosimilar substitution provides a good model for states that have not yet passed such legislation. Part I reviews state laws regulating the substitution of generic, small-molecule drugs for brand-name drugs. Part II provides some background information on biologic drugs and biosimilars. Part III considers five provisions that often appear in existing state legislation on biosimilar substitution: interchangeability, indications to “Dispense as Written,” physician communication, patient notification, and recordkeeping. Part III goes on to argue that states should include all of these provisions in their biosimilar substitution laws, except that patient-notification provisions should not permit patients to opt out unless they have a legitimate medical reason.

## I. STATE LAWS FOR GENERIC SUBSTITUTION

Before turning to how states should regulate the substitution of biosimilars for biologic drugs, it may be helpful to examine first how states regulate the substitution of generic, small-molecule drugs for brand-name drugs.<sup>13</sup> After all, the easiest way for a state to regulate biosimilar substitution would be to copy as many of its provisions about generic drugs as possible. But examining these laws for generic drug substitution might also reveal areas where biosimilar substitution must necessarily differ.

Although substitution laws for generic drugs are well-established across the entire United States, states handle these laws in different ways. This Part reviews state laws governing the substitution of generic drugs for their brand-name equivalents. It surveys several provisions common among state laws and explains how those laws differ across jurisdictions.

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9. See *infra* Part II.

10. See *infra* Part III.

11. Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, NAT’L CONFERENCE OF STATE LEGISLATURES (Dec. 1, 2017), <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>.

12. For an explanation of what makes a biosimilar “interchangeable,” see *infra* text accompanying notes 66–70.

13. Readers who understand the intricacies of generic drug substitution but are not as familiar with biologic drugs should feel free to skip ahead to Part II.

All fifty states have enacted laws that regulate how pharmacists substitute generic, small-molecule drugs for brand-name drugs.<sup>14</sup> State laws differ, however, on whether substitution is mandatory or merely permissive.<sup>15</sup> Currently, fourteen states require pharmacists to substitute generic drugs for brand-name drugs whenever generic drugs are available.<sup>16</sup> The remaining states mostly allow pharmacists to substitute generic drugs for brand-name drugs at their discretion.<sup>17</sup> Accordingly, one might expect that patients in states with mandatory substitution laws receive generic drugs more frequently than patients in states with only permissive substitution laws.<sup>18</sup>

Regardless of whether generic substitution is mandatory or permissive, states use a few different approaches for determining whether substitution is appropriate. Some states use positive or negative drug formularies.<sup>19</sup> Positive formularies identify which drugs pharmacists may (or must) substitute, whereas negative formularies indicate which drugs pharmacists may (or must) not substitute.<sup>20</sup> Most states, however, do not use the formulary approach.<sup>21</sup> In those states, pharmacists simply “must ensure that substitutions are made within the requirements of the state law.”<sup>22</sup>

Whether or not they use formularies, some states rely on the FDA to determine whether generic drugs are therapeutically equivalent to brand-name drugs.<sup>23</sup> The FDA publishes a list known as the “Orange Book,” which identifies generic drugs that it has deemed “therapeutically equivalent to other pharmaceutically equivalent products.”<sup>24</sup> According to the FDA, “products classified as therapeutically equivalent can be substituted with the

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14. NAT'L ASS'N OF BDS. OF PHARMACY, SURVEY OF PHARMACY LAW 71–74 (2017) [hereinafter SURVEY OF PHARMACY LAW].

15. *Id.* at 71.

16. The jurisdictions with mandatory substitution laws comprise a geographically and politically diverse group: Florida, Kansas, Kentucky, Massachusetts, Minnesota, Mississippi, Nevada, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Washington, and West Virginia. *See id.*

17. *Id.*

18. Insurers might complicate this picture by deciding to cap reimbursements at certain rates or using formularies to encourage filling prescriptions with generic drugs. *See* Charles Ornstein & Katie Thomas, *Prescription Drugs May Cost More with Insurance than Without It*, N.Y. TIMES (Dec. 9, 2017), <https://www.nytimes.com/2017/12/09/health/drug-prices-generics-insurance.html> (noting that insurers make some drugs more expensive than they would otherwise be). These concerns, while important, are generally beyond the scope of this Note.

19. SURVEY OF PHARMACY LAW, *supra* note 14, at 71.

20. Robert W. Piepho, *Substitution at the Pharmacy Level*, MEDSCAPE (Nov. 10, 2000), [http://www.medscape.org/viewarticle/416390\\_4](http://www.medscape.org/viewarticle/416390_4).

21. SURVEY OF PHARMACY LAW, *supra* note 14, at 71.

22. Piepho, *supra* note 20.

23. SURVEY OF PHARMACY LAW, *supra* note 14, at 71, 73.

24. *Orange Book Preface*, U.S. FOOD & DRUG ADMIN. § 1.7 (June 10, 2016), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>. The Orange Book also includes information on patents and regulatory exclusivity for small-molecule drugs. *Id.* § 1.1. Those limited monopolies are beyond the scope of this Note.

full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.”<sup>25</sup> But despite the FDA’s expertise regarding therapeutic equivalence, the ultimate authority to regulate substitution rests with the state.<sup>26</sup>

States have devised a range of ways in which physicians may indicate that generic drugs should not be substituted for prescribed, brand-name drugs. Substitution would be inappropriate, for example, where a generic drug contains an inactive ingredient that is not in the brand-name drug and that the patient cannot tolerate.<sup>27</sup> In states that have opted to use a two-line prescription format, physicians sign on a line indicating that pharmacists may substitute generic drugs for brand-name products.<sup>28</sup> In states without two-line prescription formats, physicians typically must write a phrase like “Brand Medically Necessary,” “Dispense as Written,” or “Do Not Substitute” on prescriptions to prevent generic substitutions.

Under all of these systems, some physicians instinctively require that pharmacists dispense brand-name drugs even when generic drugs may be appropriate.<sup>29</sup> In response, some states have begun requiring physicians to write down why prescriptions must be filled with brand-name drugs.<sup>30</sup> After passing such a law, Massachusetts saw a “dramatic” decrease of \$150 million in its Medicaid spending.<sup>31</sup> Encouraging substitution whenever possible allows states to realize the full benefits of generic drugs.

States differ on whether generic substitution requires patient awareness.<sup>32</sup> Most states require patient awareness in some form. Patient awareness can be attained either through approval *before* pharmacists fill prescriptions or through notification *after* pharmacists fill prescriptions.<sup>33</sup>

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25. *Id.* § 1.2.

26. *See* United States v. Evers, 643 F.2d 1043 (5th Cir. 1981) (noting that federal law is “not intended to regulate the practice of medicine”).

27. *See* Beth Levine, *The Truth About Generic vs. Brand-Name Medications*, HUFFINGTON POST (Feb. 22, 2015, 9:11 AM), [https://www.huffingtonpost.com/2015/02/22/generic-prescriptions\\_n\\_6730194.html](https://www.huffingtonpost.com/2015/02/22/generic-prescriptions_n_6730194.html) (noting that a patient might have an allergic reaction to one generic drug but not to another generic drug with the same active ingredient); *see also* Tina Zerilli et al., *To Substitute or Not to Substitute: That Is the Question*, PHARMACY TIMES (Mar. 14, 2011), <http://www.pharmacytimes.com/publications/issue/2011/march2011/genericfeature-0311> (listing some generic drugs for which bioequivalence has been disputed).

28. SURVEY OF PHARMACY LAW, *supra* note 14, at 71, 73.

29. Ranit Mishori, *Some Doctors Insist on Brand-Name Drugs Even When Cheaper Generics Are Available*, WASH. POST (July 11, 2011), [http://www.washingtonpost.com/national/some-doctors-insist-on-brand-name-drugs-even-when-cheaper-generics-are-available/2011/06/13/gIQAmCOL9H\\_story.html?tid=a\\_inl](http://www.washingtonpost.com/national/some-doctors-insist-on-brand-name-drugs-even-when-cheaper-generics-are-available/2011/06/13/gIQAmCOL9H_story.html?tid=a_inl) (noting \$7.7 billion in excess healthcare costs per year).

30. *Id.* (“While some states require pharmacists to offer generic equivalents unless a doctor specifies ‘Dispense as Written,’ a few jurisdictions are moving to limit the DAW override.”).

31. *Id.*

32. SURVEY OF PHARMACY LAW, *supra* note 14, at 71.

33. *Id.* at 71 n.\*\*.

For example, Colorado requires that patients be notified both orally and in writing.<sup>34</sup> But there are still sixteen states where patient awareness is not necessarily required.<sup>35</sup> The end result is that not all patients who take generic drugs will know that they are taking generics.

Some state generic substitution laws are more cost-conscious than others. Because the major goal of generic substitution is to reduce healthcare costs, most states require that dispensed generics be cheaper, or at least no more expensive than, the prescribed brand-name drugs.<sup>36</sup> Approximately a dozen states even require that full cost savings must be passed on to patients.<sup>37</sup> But the remaining states do not have any provisions discussing cost savings.<sup>38</sup>

New York's law on generic substitution illustrates some of the typical provisions in this kind of legislation. Under New York's generic substitution law, prescribers must write "d a w" for "dispense as written" in a box on a prescription pad to mandate that pharmacists fill prescriptions with brand-name drugs.<sup>39</sup> Otherwise, "the prescriber's signature . . . shall designate approval of substitution" with generic drugs.<sup>40</sup> Substitution is not required, however, if pharmacists offer the brand-name drugs at the same prices as generic drugs.<sup>41</sup> In emergency situations, brand-name drugs may be dispensed at their normal prices if generic drugs are not available.<sup>42</sup> Finally, prescribers must tell the patient whether brand-name or generic drugs have been prescribed.<sup>43</sup>

Generic substitution laws remain robust across the United States.<sup>44</sup> But one practical implication of having states with different generic substitution laws is that patients with the same prescriptions may end up taking different brand-name or generic drugs, i.e., different formulations of the same active ingredient. Plus, patients with the same prescriptions in different states may have significantly different interactions with their pharmacists. As states adapt their laws to account for biologic drugs, one might wonder whether biosimilar substitution laws should diverge more or less from one another than generic substitution laws.

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34. *Id.* at 71, 74.

35. *Id.* at 71, 73–74.

36. *Id.*

37. *Id.*

38. *Id.*

39. N.Y. EDUC. LAW § 6810(6)(a) (McKinney 2016).

40. *Id.*

41. *Id.*

42. An emergency situation is defined as a situation involving "any condition requiring alleviation of severe pain or which threatens to cause disability or take life if not promptly treated." *Id.*

43. EDUC. § 6810(6)(b).

44. See SURVEY OF PHARMACY LAW, *supra* note 14, at 71–72 (comparing provisions across all fifty states, D.C., Guam, and Puerto Rico).

## II. BIOLOGIC DRUGS & BIOSIMILARS

With systems for generic substitution in place, states have long accepted generic drugs as familiar options within the healthcare system. But advances in modern medicine have revolutionized the drugs that some patients now receive. Biologic drugs and biosimilars differ from brand-name, small-molecule drugs and generic drugs in significant ways. Crucially, biosimilars are not merely generic biologic drugs. State laws for biosimilar substitution must account for the differences between generic drugs and biosimilars. This Part provides some necessary background information on biologic drugs and biosimilars. It also explains how the federal government regulates approval of biosimilars.

Biologic drugs differ from small-molecule drugs in important ways. Whereas chemists synthesize small-molecule drugs using conventional laboratory techniques,<sup>45</sup> scientists must generate “protein-based” biologics “using DNA technology.”<sup>46</sup> In other words, “a biologic comes from a living organism” rather than “a set recipe” of chemicals.<sup>47</sup> The resulting biologic drugs are “complex macromolecular entities comprised of sugars, proteins, or nucleic acids” in which the three-dimensional configuration is especially important.<sup>48</sup> Because of their complexity, biologic drugs are many times more expensive than small-molecule drugs.<sup>49</sup> But, despite their cost, biologic drugs have proven particularly helpful for combatting serious diseases and conditions that significantly lower patients’ quality of life, like cancer, arthritis, and autoimmune disorders.<sup>50</sup>

Given the success of biologic drugs, competing manufacturers have grown increasingly interested in bringing follow-on products, called “biosimilars,” to market. These copycat biologics “are similar, but not identical, to the biologics for which they will be substituted.”<sup>51</sup> Under current limitations of science, similarly designed biological products may have slightly

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45. See *supra* note 5.

46. Stacey L. Worthy & John F. Kozak, *Follow-On Biologics: Protecting Consumers Through the State Pharmacy Law in Light of FDA Actions*, 17 QUINNIPIAC HEALTH L.J. 207, 207–08 (2014).

47. Lindsay Kelly, *Biologics in the Practice of Law*, 39 HARV. J.L. & PUB. POL’Y 21, 21 (2016); see also Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J.L. & MED. 49, 63 (2015) (“Biological products are derived from living materials, including viruses, therapeutic serums, toxins and antitoxins, vaccines, blood and blood products, and cells, tissues, and gene therapy products.”).

48. Paradise, *supra* note 47, at 64; see also W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1026 (2016) (“In terms of size and rough complexity, if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet.”).

49. Paradise, *supra* note 47, at 51 (noting that, on average, biological drugs are “twenty-two times the price of traditional drugs”).

50. See Kelly, *supra* note 47, at 21; Worthy & Kozak, *supra* note 46, at 208.

51. Kelly, *supra* note 47, at 23.



different structures.<sup>52</sup> Considering the parallels with small-molecule drugs, it may be enticing to view biosimilars as generic biologic drugs. But because biosimilars are not identical to their corresponding biologic drugs, also known as “reference products,” viewing biosimilars merely as generic biologic drugs is misguided.<sup>53</sup>

Under federal law, the FDA’s process for approving biologic drugs and biosimilars differs from its process for approving small-molecule drugs and their generics. The FDA approves new small-molecule drugs under procedures outlined in the Food, Drug & Cosmetic Act (FDCA),<sup>54</sup> and it approves generics under amendments called the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act).<sup>55</sup> The FDCA and the Hatch-Waxman Act do not, however, address biologic drugs and biosimilars. Instead, the FDA approves biologic drugs under the Public Health Service Act (PHSA).<sup>56</sup> Until Congress passed the ACA in 2010,<sup>57</sup> the FDA did not have a mechanism for approving biosimilars.<sup>58</sup> As part of the ACA, Congress passed the Biologics Price Competition and Innovation Act (BPCIA), which amended the PHSA so that the FDA could grant licenses for new biosimilars.<sup>59</sup>

The BPCIA sets out the requirements that a biosimilar Biologics License Application (bBLA) must meet for FDA approval.<sup>60</sup> Under the statute, a bBLA must include:

- (aa) analytical studies that demonstrate that the biological product is highly similar to the reference product. . . ;
- (bb) animal studies (including the assessment of toxicity); and
- (cc) a clinical study or studies . . . that are sufficient to demonstrate safety, purity, and potency.<sup>61</sup>

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52. Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 59 (2012).

53. See Kelly, *supra* note 47, at 21 (“[T]here can be no ‘generic’ biologic.”).

54. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

55. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 U.S.C.).

56. Pub. L. No. 78-410, 58 Stat. 682 (1944) (codified as amended in scattered sections of 42 U.S.C.).

57. Pub. L. No. 111-148, 124 Stat. 119 (2010) (codified as amended in scattered sections of 26 and 42 U.S.C.).

58. See Kelly, *supra* note 47, at 22.

59. Paradise, *supra* note 47, at 64–65.

60. See *id.* Although Paradise uses the “bBLA” terminology, the BPCIA generally refers to “an application under subsection (k).” *E.g.*, 42 U.S.C. § 262(i)(2) (2012). I also use the term “bBLA” for simplicity.

61. 42 U.S.C. § 262(k)(2)(A)(i)(I).

According to the bBLA, the biosimilar must work via the same mechanism of action as the reference product,<sup>62</sup> and the biosimilar's proposed use must be the same as one of the reference product's uses.<sup>63</sup> Additionally, "the route of administration, the dosage form, and the strength" of the biosimilar must match the reference product.<sup>64</sup> The FDA publishes a list of all approved biosimilars in the "Purple Book."<sup>65</sup>

The FDA may deem biosimilars that are highly similar to their reference products as "interchangeable." The BPCIA defines an interchangeable biosimilar as one that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."<sup>66</sup> For the FDA to deem a biosimilar interchangeable, the bBLA must show that the drug "can be expected to produce the same clinical result as the reference product in any given patient."<sup>67</sup> Additionally, when patients are meant to take the same biologic drug more than once, patients must be able to switch back and forth between an interchangeable biosimilar and the reference product without any additional risk.<sup>68</sup> In making its determinations regarding interchangeability, the FDA uses a "totality of the evidence" approach that it will undoubtedly refine as it gains experience with these applications.<sup>69</sup> It also publishes its interchangeability determinations in the Purple Book.<sup>70</sup>

Biosimilars are starting to enter the market. In 2015, the FDA approved its first biosimilar, which was approved in Europe in 2009.<sup>71</sup> The drug, Sandoz's Zarxio, is similar to Amgen's Neupogen and is intended to prevent

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62. 42 U.S.C. § 262(k)(2)(A)(i)(II).

63. 42 U.S.C. § 262(k)(2)(A)(i)(III).

64. 42 U.S.C. § 262(k)(2)(A)(i)(IV).

65. *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. FOOD & DRUG ADMIN. (Sept. 15, 2017) [hereinafter *Purple Book*], <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>; see also LIST OF LICENSED BIOLOGICAL PRODUCTS WITH (1) REFERENCE PRODUCT EXCLUSIVITY AND (2) BIOSIMILARITY OR INTERCHANGEABILITY EVALUATIONS TO DATE, U.S. FOOD & DRUG ADMIN. 1–3 (2017) [hereinafter LIST OF LICENSED BIOLOGICAL PRODUCTS], <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf>.

66. 42 U.S.C. § 262(i)(3).

67. 42 U.S.C. § 262(k)(4)(A)(ii).

68. 42 U.S.C. § 262(k)(4)(B).

69. See Kanter & Feldman, *supra* note 52, at 60 ("[T]he FDA released several draft guidances in February 2012. . . . They outline the FDA's 'totality of the evidence' approach to biosimilar approval. . .").

70. See LIST OF LICENSED BIOLOGICAL PRODUCTS, *supra* note 65.

71. Sabrina Tavernise & Andrew Pollack, *F.D.A. Approves Zarxio, Its First Biosimilar Drug*, N.Y. TIMES (Mar. 6, 2015), <http://www.nytimes.com/2015/03/07/health/fda-approves-zarxio-first-biosimilar-drug.html>.

infections in those undergoing chemotherapy.<sup>72</sup> Since Zarxio, the FDA has approved a handful of other biosimilar applications.<sup>73</sup> For example, the FDA approved a biosimilar version of Johnson & Johnson's Remicade in April 2016.<sup>74</sup> So far, the FDA has not deemed any of the approved biosimilars as interchangeable.<sup>75</sup> Despite the slow start, "[t]hings now seem to be heating up," and drug manufacturers are currently sponsoring approximately sixty clinical trials aimed at gaining approval for new biosimilars.<sup>76</sup> As more and more biosimilars enter the market, the need for states to pass biosimilar substitution laws continues to grow.<sup>77</sup>

### III. STATE BIOSIMILAR SUBSTITUTION LAWS

With the advent of biosimilars, states must reconsider how substitution laws work for significantly different classes of drugs.<sup>78</sup> This Part examines five features of biosimilar substitution legislation: interchangeability, indications to "Dispense as Written," physician communication, patient notification, and recordkeeping. This Part goes on to argue that states should embrace these provisions, provided that they do not allow patients to opt out of substitution without a legitimate medical reason. These recommendations are most relevant for states that have yet to pass biosimilar substitution laws, but even states that have already passed such laws could still amend them before the FDA designates a biosimilar as interchangeable.

States began passing biosimilar substitution laws only a few years ago. Eight states led the way in 2013 and 2014,<sup>79</sup> and seventeen states followed

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72. *Id.*

73. See LIST OF LICENSED BIOLOGICAL PRODUCTS, *supra* note 65, at 1–3 (indicating seven total biosimilar approvals).

74. Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions*, N.Y. TIMES (July 15, 2016), <http://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html>.

75. See LIST OF LICENSED BIOLOGICAL PRODUCTS, *supra* note 65, at 1–3 (making no indications for interchangeable biosimilars).

76. Pollack, *supra* note 74.

77. See Zachary Brennan, *FDA: Interchangeable Biosimilar Approvals Expected Within 2 Years*, REGULATORY AFFAIRS PROF'L SOC'Y (June 26, 2017), <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/6/fda-interchangeable-biosimilar-approvals-expected-within-2-years> (noting that the FDA expects interchangeable biosimilars to hit the market soon).

78. For a broader view of how states might handle the relationship between generic drug and biosimilar substitution laws, see generally Brian F. King, *Emerging Market for Biosimilars: State Legislation Should Reconcile Biosimilar Substitution Laws with Existing Laws on Generic Substitution*, 18 DEPAUL J. HEALTH CARE L. 31 (2016).

79. Cauchi, *supra* note 11. Like the group of states with mandatory generic substitution laws instead of permissive substitution laws, see *supra* note 16, this cohort of leading states is geographically and politically diverse: Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, Utah, and Virginia. See Cauchi, *supra* note 11.

their lead in 2015 and 2016.<sup>80</sup> In 2017, an additional eleven states passed biosimilar substitution laws.<sup>81</sup> Legislatures in eight states proposed bills that ultimately failed.<sup>82</sup> Only six states have not yet considered biosimilar substitution laws at all.<sup>83</sup> The laws already on the books typically contain provisions related to biosimilars' interchangeability, the prescriber's ability to block substitution, communication between the pharmacist and the prescriber, patient notification, and recordkeeping.<sup>84</sup>

Interested parties have lobbied the states to enact laws with provisions that favor their respective sides.<sup>85</sup> Manufacturers of innovator biologic drugs have asked states to pass biosimilar substitution laws that would generally restrict pharmacists.<sup>86</sup> At the same time, biosimilar manufacturers have argued for fewer restrictions on pharmacists.<sup>87</sup> Lobbying efforts continue as both sides encourage state legislatures to adopt policies that would benefit sales of their brand-name biologic drugs or biosimilars.<sup>88</sup>

#### A. *Interchangeability*

Not all states impose requirements for the interchangeability of biosimilars.<sup>89</sup> Some states with biosimilar substitution laws insist that biosimilars meet the FDA's requirements for interchangeability before they can be substituted for their reference products.<sup>90</sup> For example, Missouri law states that a "pharmacist filling prescription orders for drug products prescribed by trade or brand name may select another drug product . . . of the same . . . *interchangeable* biological product type, as . . . accepted by the Federal

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80. Those states are Arizona, California, Colorado, Georgia, Hawaii, Idaho, Illinois, Kentucky, Louisiana, Missouri, New Jersey, North Carolina, Pennsylvania, Rhode Island, Tennessee, Texas, and Washington. *Id.*

81. These recent actors are Iowa, Kansas, Maryland, Minnesota, Montana, Nebraska, Nevada, New Mexico, New York, Ohio, and South Carolina. *Id.*; see also *Senate Bill S4788A*, N.Y. STATE SENATE, <https://www.nysenate.gov/legislation/bills/2017/s4788/amendment/a> (last visited Jan. 11, 2018) (noting that the governor signed New York's pending bill).

82. Those states are Alabama, Alaska, Arkansas, Connecticut, Michigan, Mississippi, Oklahoma, and Vermont. Cauchi, *supra* note 11.

83. The following states have not yet acted: Maine, New Hampshire, South Dakota, West Virginia, Wisconsin, and Wyoming. *Id.*

84. See *id.* (comparing state law provisions).

85. See Pollack, *supra* note 8 (characterizing Virginia's law as influenced by these lobbying efforts).

86. *Id.* (discussing lobbying efforts by Amgen and Genentech, including giving copies of proposed bills to state legislators).

87. See *id.* ("Generic drug companies and insurers are taking their own steps to oppose or amend the state bills, which they characterize as pre-emptive moves to deter the use of biosimilars. . .")

88. See *id.* ("The trench fighting at the state level is the latest phase in a battle over the rules for adding competition to the biotechnology drug market. . .")

89. SURVEY OF PHARMACY LAW, *supra* note 14, at 72.

90. *Id.* at 72–74.

Food and Drug Administration.”<sup>91</sup> In the BPCIA, Congress specified criteria for the FDA to consider when it decides whether biosimilars are interchangeable.<sup>92</sup> In fact, the BPCIA specifically contemplates substitution by defining an interchangeable biosimilar as one that “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”<sup>93</sup>

Moving forward, states should require pharmacists to rely on the FDA’s determinations of interchangeability. Simply put, the FDA has unmatched scientific expertise in the area of biologic drugs. Unlike generic drugs, whose applications only require proof of bioequivalence, bBLAs require at least one clinical trial.<sup>94</sup> The FDA has tremendous experience evaluating data from clinical trials, while states do not. Because biosimilars are new and more complicated than generic, small-molecule drugs,<sup>95</sup> states should not attempt to make their own determinations of which ones may be substituted for their reference products. Years from now, once scientists better understand biologic products, states might consider adopting a formulary approach for biosimilars.<sup>96</sup> But in the meantime, states should defer to the FDA to reach the best clinical results.

#### B. Prescriber Prohibitions on Substitution

State laws generally agree that prescribers should be able to block the substitution of biosimilars for prescribed biologic drugs.<sup>97</sup> Like the mechanisms for blocking generic substitution,<sup>98</sup> standard procedure is for a physician to check a box or to write a phrase like “Brand Medically Necessary” on the face of the prescription. For example, Missouri law establishes a two-line format for prescriptions where physicians sign on a line marked “Dispense as Written” to block substitution of a biosimilar for its reference product.<sup>99</sup> This mechanism provides the physician with a great deal of control over which medication her patient will receive.

States that have not yet passed biosimilar substitution laws should include a provision that allows physicians to block substitutions when medically necessary. As with all provisions in biosimilar substitution laws, this provision stems from concerns for patients’ safety. It ensures that patients

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91. MO. ANN. STAT. § 338.056(1) (West 2016) (emphasis added).

92. See *supra* Part II.

93. 42 U.S.C. § 262(i)(3) (2012).

94. 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc)(2012).

95. See *supra* Part II.

96. See *supra* text accompanying notes 19–20.

97. See Paradise, *supra* note 47, at 77, 78 fig. 1 (discussing the first eight biosimilar substitution laws).

98. See *supra* Part I.

99. MO. ANN. STAT. § 338.056(2) (West 2016). The entire statutory section, including this opt-out provision, covers both generic drugs and interchangeable biological products. § 338.056.

who may not tolerate biosimilars as well as reference products will not suffer from avoidable side effects.<sup>100</sup> Patients and physicians know patients' medical histories best, and physicians should be able to prevent any increased risks to patients.

But states that have not yet passed biosimilar substitution laws should also include provisions requiring physicians to explain why reference products must be dispensed instead of biosimilars. Unfortunately, some physicians instinctively indicate that prescriptions should be dispensed as written even when brand-name products are not medically necessary.<sup>101</sup> Almost one half of doctors participating in a survey "acknowledged holding some negative perceptions about the quality of generic medications," even despite a lack of evidence that such drugs are inferior.<sup>102</sup> Given Massachusetts's success in amending its generic substitution laws to require doctors to explain why brand-name drug are medically necessary,<sup>103</sup> states should adopt the same policy for biosimilars. This provision would prevent doctors from reflexively writing prescriptions for reference products without thoughtfully considering substitution. Where medically necessary, patients would still be able to receive reference products, but this provision would help states maximize the benefits of biosimilar substitution.

### C. *Communication with Prescribers*

There is a consensus among states that have already passed biosimilar substitution laws that those laws should include provisions requiring pharmacists to provide information about substitutions to prescribing physicians.<sup>104</sup> When states passed the first biosimilar substitution bills, legislatures required pharmacists to notify prescribers of any substitution.<sup>105</sup> Now, the laws typically specify that the pharmacist must "communicate with" the physician about the substitution.<sup>106</sup> For example, Massachusetts law prefers that pharmacists communicate with physicians by noting any biosimilar substitutions in patients' "interoperable electronic health record[s]."<sup>107</sup> Communication does not slow down pharmacy transactions in the same way that

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100. See *supra* note 27 and accompanying text.

101. Mishori, *supra* note 29.

102. *Id.*

103. See *supra* notes 30–31 and accompanying text.

104. See Cauchi, *supra* note 11.

105. *Id.* ("In bills enacted in 2013-2014, the language usually required that the prescriber 'must be notified' of any allowable substitution made at a pharmacy.").

106. *Id.* ("[T]he language commonly has been adjusted to say 'communicate with,' allowing a notation in an electronic medical record (EMR), PBM records or [a] 'pharmacy record that can be electronically accessible by the prescriber.'").

107. MASS. GEN. LAWS ANN. ch. 112, § 12EE(d) (West 2016) (when a pharmacy is not equipped with interoperable electronic health records, the statute directs pharmacists to communicate with physicians by other means).

notification might, which allows patients to receive necessary medications faster.<sup>108</sup>

The consensus on this provision is largely due to lobbying efforts by both sides. Although interest groups for reference product and biosimilar manufacturers disagree on many aspects of biosimilar regulation, they have reached a compromise on communication. The Biotechnology Industry Organization (BIO) and the Generic Pharmaceutical Association (GPhA) agreed to the following language for proposed statutes: “[W]ithin a reasonable time following the dispensing of a biological product, the dispensing pharmacist . . . shall communicate to the prescriber the specific product provided to the patient.”<sup>109</sup> Like many statutes, language in the Massachusetts statute largely mirrors this suggested wording.<sup>110</sup>

States would be wise to continue following this compromise. Generally, reference product and biosimilar manufacturers are diametrically opposed on substitution laws; biosimilar companies want substitution to be as easy as possible, while reference product companies want to restrict substitution.<sup>111</sup> Their agreement on this issue signals that both sides believe this information is required to protect patient safety.<sup>112</sup> Doctors must know precisely which medications their patients have taken in order to report adverse events, and they need that information if patients must later take similar drugs. This requirement is not controversial because physicians are better trained than patients to understand the differences between reference products and biosimilars.

#### D. Notifications for Patients

States are divided over whether pharmacists must notify patients when they substitute biosimilars for reference products.<sup>113</sup> For example, Massachusetts law requires pharmacists to notify patients after substitutions.<sup>114</sup> Other states require pharmacists to alert patients *before* the substitutions oc-

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108. See Cauchi, *supra* note 11 (“This would allow a physician to assess and compare the patient experience, but not delay the transaction.”).

109. Paradise, *supra* note 47, at 80 (quoting Randi Hernandez, *Industry Players Reach Compromise on Biosimilar Substitution*, BIOPHARM INT’L (Dec. 12, 2014), <http://www.biopharminternational.com/industry-players-reach-compromise-biosimilar-substitution>). Since this agreement, GPhA changed its name to the Association for Accessible Medicines (AAM).

110. See § 12EE(d) (“Within a reasonable time following any such substitution, the dispensing pharmacist . . . shall notify the prescribing practitioner of the substitution.”).

111. See Pollack, *supra* note 8.

112. This requirement could potentially generate valuable data, providing an ulterior motive for BIO and AAM. But it is not clear how useful or accessible such data would be, and this possibility would not delegitimize their patient safety concerns.

113. Cauchi, *supra* note 11.

114. § 12EE(e) (“Following any such substitution, the dispensing pharmacist . . . shall notify the patient . . . of the substitution. The notification shall be written and may be conveyed by facsimile, electronic transmission, a notation in the patients record system shared with the prescriber or another means consistent with prevailing pharmacy practice. . .”).

cur.<sup>115</sup> Virginia law, for instance, requires that pharmacists inform patients “prior to dispensing the interchangeable biosimilar[s],” presumably giving patients opportunities to object.<sup>116</sup> These provisions seem motivated by the idea that patients have a right to complete information about their healthcare.

At the opposite extreme, a few states do not require pharmacists to notify patients at all.<sup>117</sup> North Carolina is part of this minority.<sup>118</sup> Legislators might justify omitting such a provision because most consumers do not understand the difference between biosimilars and reference products. Others might reason that, despite the lack of a provision, pharmacists might voluntarily provide the information to patients anyway. Overall, patients in some states may become familiar with biosimilars, whereas patients in other states may remain clueless.

States should not require pharmacists to receive patient approvals before dispensing biosimilars. Patients might instinctively refuse biosimilars without understanding the underlying science. For example, some patients might believe that biosimilars are not as safe or effective as their reference products.<sup>119</sup> But if biosimilars must be deemed interchangeable by the FDA before they can be substituted,<sup>120</sup> patient concerns about safety and efficacy would be unfounded. Also, patients might reject biosimilars simply because they recognize reference products’ brands. Preventing substitution in those cases would be wasteful. Biosimilar substitution has the potential to save the healthcare system from significant, unnecessary costs.<sup>121</sup> Requiring patient approval for substitution, however, might prevent states from realizing the full benefits of biosimilars.

States should, however, require that pharmacists provide patients with information about the substituted products that they receive. This information could be conveyed, for example, through the labels accompanying biosimilars. Of course, patients might not read this information; they might only care whether the medication works.<sup>122</sup> But for those who do wish to learn more, labels would be informative. To be most helpful, the language on these labels should be in layman’s terms. This information would provide a good starting point for patients who want to discuss continuing treatment

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115. Cauchi, *supra* note 11.

116. VA. CODE ANN. § 54.1-3408.04 (2016).

117. *See* Cauchi, *supra* note 11.

118. *See* N.C. GEN. STAT. § 90-85.28 (2016) (making no mention of any patient notification requirement).

119. *See supra* text accompanying note 102.

120. *See supra* Section III.A.

121. *See supra* note 8 and accompanying text.

122. Patients might also not read drug labels because they find the sheer amount of information in those labels overwhelming. *See* Ind. Univ. Sch. of Med., *Information Overload in Drug Side Effect Labeling*, SCIENCE DAILY (May 24, 2011), <https://www.sciencedaily.com/releases/2011/05/110523171058.htm> (noting that the average drug label contains 70 different side effects).



options with their doctors. Overall, states should encourage pharmacists to provide patients with complete information about their treatment without confusing those patients.

### E. Recordkeeping

States mostly agree that pharmacists and physicians should keep records on which biosimilars are substituted for which patients.<sup>123</sup> Generally, states require that pharmacies keep records for at least a couple of years.<sup>124</sup> On one end of the spectrum, Massachusetts only requires pharmacies to keep records of biosimilar substitutions for one year.<sup>125</sup> On the other end of the spectrum, Missouri law requires that pharmacies retain records for at least five years.<sup>126</sup> However, Idaho does not require retention of *any* pharmacy records on biosimilar substitution.<sup>127</sup> Idaho law only requires that the biosimilar's "name . . . and the manufacturer or the NDC number [are] documented in the patient medical record."<sup>128</sup> Variations in these provisions mean that physicians, pharmacists, and patients in different states might have different access to historical prescription information.

States should require pharmacies to keep records on biosimilar substitutions for at least as long as they currently require pharmacies to keep records on generic substitutions. Biosimilar substitution records should not be overly burdensome to maintain because states already keep track of generic substitutions.<sup>129</sup> These records also have the potential to help medical researchers. For example, records may provide a bank of useful data for institutions conducting research on the successes and drawbacks of substituting biosimilars for their reference products.<sup>130</sup> Retaining records is administratively feasible, and it could help states protect their residents' health.

Ideally, states should require pharmacies to retain records for biosimilar substitution even longer than records for generic substitution. Generic drugs

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123. Cauchi, *supra* note 11.

124. *See id.*

125. MASS. GEN. LAWS ANN. ch. 112, § 12EE (West 2016) ("The dispensing pharmacist . . . shall retain a record of each substitution, for *not less than 1 year* from the date of the last entry in the profile record, of an interchangeable biological product dispensed." (emphasis added)).

126. MO. ANN. STAT. § 338.100(1) (West 2016) ("Every . . . pharmacy shall cause to be kept in a uniform fashion . . . a suitable book, file, or electronic record-keeping system in which shall be preserved, for a period of *not less than five years*, the original or order of each drug or biological product which has been compounded or dispensed at such pharmacy. . . ." (emphasis added)).

127. *See* IDAHO ADMIN. CODE r. 27.01.01.130 (2016).

128. *Id.*

129. *See, e.g.,* MO. ANN. STAT. § 338.100(1) (West 2016) (requiring pharmacies to keep "a suitable book, file, or electronic record-keeping system . . . for a period of not less than five years").

130. Again, it is not entirely clear how easily data could be integrated into clinical studies. *See supra* note 112.

have been studied extensively, but there are some open questions about biosimilars. History has shown that drugs' long-term side effects may not become evident until they enter the market.<sup>131</sup> Because biosimilars are more complex molecules than generic drugs,<sup>132</sup> states should monitor them closely while encouraging their use. Maintaining accurate records is a small but necessary step toward achieving that goal.

In sum, when it comes to biosimilar substitution laws, states should adopt provisions on interchangeability, prescribers' ability to prevent substitution, communication with prescribers, notification of patients, and record-keeping. Those provisions should be finely tuned to protect current patients' safety while promoting future patients' health.

#### CONCLUSION

The advent and approval of biosimilars presents the United States with novel scientific and legal problems. In light of congressional action and FDA regulation, some states have already passed laws to address biosimilars. States that have not yet passed biosimilar substitution laws should look to current state legislation for guidance. They should embrace provisions regarding interchangeability, prescriber prohibitions on substitution, communication with prescribers, and recordkeeping while rejecting overly burdensome provisions regarding patient pre-approval. States that have already enacted biosimilar substitution laws may still learn from these lessons before the FDA deems the first biosimilar as interchangeable. If states find the right balance between protecting patients' safety and promoting biosimilars in the market, biosimilars have the potential to be revolutionary.

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131. See, e.g., Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES (Nov. 14, 2004), <http://www.nytimes.com/2004/11/14/business/despite-warnings-drug-giant-took-long-path-to-vioxx-recall.html> (chronicling the discovery of cardiovascular risks associated with the drug Vioxx).

132. See *supra* Part II.