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March 2017

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### Recommended Citation

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 (2017)

Available at: <https://via.library.depaul.edu/jhcl/vol18/iss1/2>

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## **EMERGING MARKET FOR BIOSIMILARS: STATE LEGISLATION SHOULD RECONCILE BIOSIMILAR SUBSTITUTION LAWS WITH EXISTING LAWS ON GENERIC SUBSTITUTION**

*Brian F. King\**

### **INTRODUCTION**

The pharmaceutical industry flourished throughout much of past two decades, creating a vast wealth of scientific knowledge and revolutionary treatments. Because of these life-saving therapies, people are living longer. Consequently, our aging population requires more medications than ever before. Who will bear the cost? Insurance companies? The government? Regardless of who picks up the tab, the true cost of healthcare will rest squarely upon the shoulders of the American people.

The cost of healthcare has become a tremendous concern that cannot be ignored. The US continues to spend a greater percentage of its wealth on healthcare than any other industrialized nation. “In 2012, the US spent an average of \$8,915 per person on health care, reaching a total of \$2.8 trillion.”<sup>1</sup> Much of this was spent on medications and a growing proportion was spent on a new class of therapies called biologics. As the market for biologics continues to grow, it becomes increasingly important for state legislation to balance the competing interests of scientific innovation and public access.

This article is intended to explore the growing market of biosimilars and to provide insight into the developing body of law. It should appeal to the interest of healthcare providers and those who have a special interest in the future of the pharmaceutical industry. After considering the recent developments in State and Federal law and the arguments for and against provisions of state legislation, this paper takes the position that, while some additional measures should be considered in

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<sup>1</sup> Katherine Wilson, *Health Care Costs 101: Slow Growth Persists*, California HealthCare Foundation, available at, <http://www.chcf.org/publications/2014/07/health-care-costs-101>. (July 2014).

state legislation to address the variability and unpredictability of biologics and biosimilars, state legislation that erects unnecessary barriers to the utilization of biosimilars will increase the cost of healthcare and will stifle innovation.

Section I provides a background to biologics, with a focus on their cost and complexity. Section II provides a brief overview of the FDA drug approval process, and an explanation of the biologic and biosimilar approval processes. Section III discusses the laws for generic substitution generally, with a focus on the status of Federal law as well as recent developments of State law that have affected the market for biosimilars. Section IV introduces the developing role of state laws and provides a survey of statements from various interest groups that depict the key arguments for and against various components of state legislation. Section V presents implications associated with the new market for biosimilars concerning the provision of healthcare and the development of new products within the pharmaceutical industry. After considering the costs and benefits of biosimilars, Section VI provides a variety of recommendations for healthcare providers, policy-makers, and stakeholders in the pharmaceutical industry as the market for biosimilars continues to develop and the accompanying body of law attempts to reconcile the public's need for access to high quality biologics and the pharmaceutical industry's incentive to invest in an unpredictable market.

## II. BACKGROUND OF BIOLOGICS

Each year, the government agency Medicare Payment Advisory Commission ("MedPAC") Biological products, like other drugs, are used for the treatment, prevention, or cure of disease in humans. In contrast to traditional chemically synthesized small molecular weight drugs, which have a well-defined structure and can be easily characterized, biological products are generally derived from living materials, which are complex in structure and usually not fully characterized.<sup>2</sup>

Biologic drugs were first developed in the 1980s and were considered so specialized that making "generic" versions was thought to be nearly impossible. But over the past 30 years, science has advanced

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<sup>2</sup> FDA, *Biosimilars: Frequently Asked Questions About Therapeutic Biological Products*, at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm> (hereinafter FDA).

dramatically, and as patents on existing biologics began to expire, drug companies sought FDA approval for close copies of patented biologics. As expected, companies with the original patents initially resisted, insisting that their products were so complex that it was impossible to copy, but with the passing of time, that argument has lost some of its steam.<sup>3</sup>

The FDA and Section 351 of the Public Health Service (PHS) Act define a biological product as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings.”<sup>4</sup>

#### *A. Complexity of Biologics*

“Biologic medicines are much more complex than traditional chemically synthesized drugs. Biologics are manufactured from living organisms by programming cell lines to produce desired therapeutic substances consisting of large, complex molecules.”<sup>5</sup> Because of their complexity, it is much more difficult to replicate biologics than traditional drugs in the manufacturing process.<sup>6</sup> Even the smallest change in the manufacturing process can have profound effects on the predictability of a product’s efficacy and safety.<sup>7</sup> Because of this, it is practically impossible to produce a generic version of a biologic that is truly identical.<sup>8</sup> “However, once patents expire for the existing brand-name biologic drugs, “biosimilar” medicines can be produced.”<sup>9</sup> Unlike generic drugs, biosimilars are not therapeutic equivalents of a reference biologic. Nor are they required to seek approval for the all of the indications or dosage forms of a reference biologic.

Because of the potential differences between biosimilars and the reference product, biosimilars are not automatically interchangeable.

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<sup>3</sup> Sabrina Traversi & Andrew Pollack, *F.D.A. Approves Zarxio, Its First Biosimilar Drug*, NEW YORK TIMES (Mar. 6, 2015).

<sup>4</sup> FDA, *Supra* note 2.

<sup>5</sup> Richard Cauchi, National Conference of State Legislatures, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*. (Sep. 10, 2015), available at <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>.

<sup>6</sup> *Id.*

<sup>7</sup> *Id.*

<sup>8</sup> *Id.*

<sup>9</sup> *Id.*

There are a number of considerations that must be addressed before a biosimilar can be classified as interchangeable. The FDA employs a “totality of evidence” approach regarding data for approval of a biosimilar, meaning that a variety of sources of data can be used for biosimilar approval. Once a biosimilar is approved, its ability to be prescribed and dispensed will be dictated by its classification as either “interchangeable” or simply “biosimilar.” Generally, products that are interchangeable can be substituted for the reference product, while biosimilars, without more, cannot.

### *B. Cost of Biologics*

In 2010, spending on biologics in the U.S. reached an astounding \$67 billion, representing nearly 30 percent of the overall prescription drug market, and displaying a much steeper growth rate than traditional drugs.<sup>10</sup> In 2013, total drug expenditure in the United States was approximately \$326 billion.<sup>11</sup> Of the top 15 drugs, 8 were biologics, representing 9% of total drug expenditure.<sup>12</sup> In fact, biologic and specialty pharmaceuticals are the fastest growing pharmaceutical expense in the US.<sup>13</sup> On average, biologic drugs are 22 times more expensive than traditional brand name drugs.<sup>14</sup>

Numerous strategies have been considered to address the growing costs of biologic medications. One strategy of cost containment has been the introduction of competing products known as biosimilars.<sup>15</sup> Biosimilars have the potential to provide considerable cost savings. The US Congressional Budget Office estimated that price competition from biosimilars would reduce total expenditures on biologics in the United States by \$25 billion over a 10-year period, with a decrease in federal

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<sup>10</sup> Michael Ollove, *More States Demand Notification to Use Biosimilar Drugs* (Mar. 30, 2015), <http://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2015/3/30/more-states-demand-notification-to-use-biosimilar-drugs>

<sup>11</sup> Univ. of Ill. at Chicago, Coll. of Pharmacy, *What is the Status of Biosimilars in the United States?* (Nov., 2014), available at <http://dig.pharm.uic.edu/faq/2014/Nov/faq1.aspx>. (hereinafter Univ. of Ill.).

<sup>12</sup> *Id.*

<sup>13</sup> James G. Stevenson, *Preparing for Biosimilars: Scientific, Regulatory, and Practice Management Issues for Pharmacists* (Dec. 12, 2012) (live webcast) available at [http://www.ashpadvantagemedia.com/downloads/handout\\_biosimilars.pdf](http://www.ashpadvantagemedia.com/downloads/handout_biosimilars.pdf).

<sup>14</sup> Anthony D. So & Samuel L. Katz, *Biologics Boondoggle*, NEW YORK TIMES, Mar. 7, 2010.

<sup>15</sup> Steven D. Lucio, *Evaluating Biosimilars for Formulary Inclusion*, PHARMACY PURCHASING & PRODUCTS, available at [http://www.pppmag.com/article\\_print.php?articleid=1591](http://www.pppmag.com/article_print.php?articleid=1591).

government spending of nearly \$6 billion.<sup>16</sup> The American Consumer Institute Center for Citizen Research estimates savings of \$250 billion in the US over the next 10 years from just 11 biosimilar products.<sup>17</sup> Therefore, there will be significant pressure in the coming years to utilize biosimilars to control health care costs.

### III. THE APPROVAL PROCESS OF GENERIC DRUGS AND BIOSIMILARS

Despite the perceived benefits of the readmission penalty, the Program has received significant criticism. The Food and Drug Administration (“FDA”) regulates traditional drugs under the Food Drug and Cosmetic Act (“FD&C Act”). In contrast, biologics are regulated under the Public Health Service (“PHS”) Act. Compared to the FD&C Act, the PHS Act gives the FDA greater regulatory control over the manufacturing processes that are uniquely important in the production of biologics.

The paragraphs that follow provide insight into the framework of the approval pathways for traditional drugs and biologic drugs, as well as a brief overview and comparison of the approval processes for generic and biosimilar counterparts respectively.

#### *A. The Food, Drug, and Cosmetic Act and Hatch-Waxman Amendments Regulate the Abbreviated Pathway for Traditional Drugs*

The FD&C Act defines an abbreviated new drug application process through which generic manufacturers can obtain approval once adequate information is offered to demonstrate bioequivalence with the reference product. Generally, these applications do not require a sponsor to conduct clinical trials. However, additional clinically related data may be required for certain products, such as immunogenicity data. For biologics, the PHS Act allows approvals via 351(a) BLA application when a sponsor demonstrates the safety, purity, and potency of an investigational product through clinical studies. The new 351(k) pathway

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<sup>16</sup> *S.1695, Biologics Price Competition and Innovation Act of 2007*, CONGRESSIONAL BUDGET OFFICE (June 25, 2008).

<sup>17</sup> Lucio, *supra* note 11.

will allow for an abbreviated approval of a biosimilar. However, unlike ANDA applications, the biosimilar pathway requires at least one clinical study to support product approval.

*B. The Public Health Service Act and Biologics Price Competition and Innovation Act Regulate the Abbreviated Pathway for Biologics*

To help reduce the cost of biologics, the Biologics Price Competition and Innovation (BPCI) Act was implemented as part of the Affordable Care Act (ACA) to allow for a streamlined approval process for biologics that are similar to existing agents, in the expectation of reducing the cost of development of these agents.<sup>18</sup> Unlike small molecule drugs, which are approved under the FD&C Act, the FDA approves most biologics under section 351 of the PHS Act. Compared to the FD&C Act, the PHS Act gives the FDA greater regulatory control over the manufacturing processes that are especially critical in the production of biologics. Just as the 1984 Hatch-Waxman amendments established the abbreviated new drug application (ANDA) for generic medications, the BPCI Act created a licensure pathway in which a follow-on product could rely on existing scientific knowledge about the originator's reference biologic.<sup>19</sup>

While the intent of the BPCI Act is similar to that of the Hatch-Waxman Amendments, the approval processes for small molecule drugs and biologics differ substantially. For example, both innovator and generic versions of traditional drugs are approved under the FD&C Act, whereas biologics are approved under the PHS Act.<sup>20</sup> While generic approvals primarily consist of bioequivalence studies only, biosimilar approvals require at least one clinical trial be conducted to demonstrate it is "highly similar" to its reference biologic.<sup>21</sup>

The Patient Protection and Affordable Care Act ("PPACA") created an approval pathway for less expensive generic versions of biologic drugs, known as biosimilars, or follow-on biologics. However, new state legislation that could greatly limit the savings from biosimilars has sparked a debate similar to the one that followed the passage of

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<sup>18</sup> Univ. of Ill., *supra* note 8.

<sup>19</sup> Lucio, *supra* note 11.

<sup>20</sup> *Preparing for Biosimilars*, Novation (Nov. 2011), available at [https://www.novationco.com/media/newsreleases/attachments/preparing\\_for\\_biosimilars.pdf](https://www.novationco.com/media/newsreleases/attachments/preparing_for_biosimilars.pdf) (hereinafter *Preparing for Biosimilars*).

<sup>21</sup> *Id.*

legislation that encouraged the development of traditional generic drugs.<sup>22</sup> The enactment of BPCI Act reflected an attempt to balance the interests of pharmaceutical manufacturers in recovering the costs of innovation and drug development with the need for patients to have access to more affordable versions of currently marketed treatments.<sup>23</sup>

Under the BPCI Act, a biological product may be classified as “biosimilar” if data show that the product is “highly similar” to or “interchangeable” with an already-approved reference biological product.<sup>24</sup> “Biosimilarity” means that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”<sup>25</sup> “Interchangeability” means that the biosimilar must produce the same expected clinical results as the reference biologic, and if the biosimilar is meant to be given more than once, it should not have a greater risk of diminished efficacy or safety concerns than the reference biologic.<sup>26</sup> If the biosimilar is interchangeable, it may be substituted with the reference biologic without intervention by the prescriber.<sup>27</sup>

Given the abbreviated nature of the approval process, biosimilars are expected to cost less than the original reference product.<sup>28</sup> However, whereas the ANDA process requires no additional clinical trial information, the complexity of biologic medications necessitates that a biosimilar application includes data substantiating that it “does not differ

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<sup>22</sup> Leigh Purvis, *A Sense of Déjà Vu: The Debate Surrounding State Biosimilar Substitution Laws*, AARP Public Policy Institute (Sept. 2014), available at [http://www.aarp.org/content/dam/aarp/research/public\\_policy\\_institute/health/2014/the-debate-surrounding-state-biosimilar-substitution-laws-AARP-ppi-health.pdf](http://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/2014/the-debate-surrounding-state-biosimilar-substitution-laws-AARP-ppi-health.pdf).

<sup>23</sup> Lucio, *supra* note 11.

<sup>24</sup> FDA, *Biosimilars*, (Mar. 6, 2015), at <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>.

<sup>25</sup> FDA, Christl Leah, *FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US* (Jan. 2, 2015) 1, 6 at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf>.

<sup>26</sup> *Id.* at 8.

<sup>27</sup> *Id.*

<sup>28</sup> Ramon Hernandez, *Biosimilar Products*, FDA (June 20, 2013) at [http://www.piapr.org/clientuploads/11th%20PIA-FDA%20RegConf%20\(June%202013\)/PP/1%20Biosimilar%20Products%20by%20R.%20Hernandez.pdf](http://www.piapr.org/clientuploads/11th%20PIA-FDA%20RegConf%20(June%202013)/PP/1%20Biosimilar%20Products%20by%20R.%20Hernandez.pdf).

in a clinically meaningful way from the reference product in terms of safety, purity, or potency.”<sup>29</sup>

Biological products are a subset of drugs that are licensed under section 351 of the PHS Act.<sup>30</sup> Because of the complexity of manufacturing and characterizing a biologic product, the PHS Act provides for a system of controls over all aspects of the manufacturing process.<sup>31</sup> It is difficult to characterize and identify the clinically active components of a complex biological product, thus such products are often defined by their manufacturing processes. “Since there is a significant difference in how biological products are made, the production is monitored by the agency during every stage of development to ensure the final product turns out as expected.”<sup>32</sup>

The PHS Act allows approval of biologics via a 351(a) BLA application when a sponsor demonstrates the safety, purity, and potency of an investigational product through clinical studies.<sup>33</sup> Prior to the creation of the biosimilar pathway under the BPCI Act, otherwise known as a 351(k) application, the 351(a) BLA application was the only biologic approval mechanism available.<sup>34</sup> The new 351(k) pathway is significant in that it allows for an abbreviated approval of a biosimilar without requiring extensive investigation and unnecessary clinical trials.<sup>35</sup>

The purpose of the 351(k) approval process is not to replicate in its entirety the clinical development actions of the originator. Instead, through a series of characterizations supported by pharmacokinetic, pharmacodynamic, and immunogenicity studies, as well as targeted clinical trial data, an applicant can prove that a product so closely resembles the originator reference biologic that the biosimilar would be expected to behave in a similar fashion in terms of safety and efficacy.<sup>36</sup> The FDA describes this process as a “totality of the evidence approach,”

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<sup>29</sup> Suzanne M. Sensabaugh, *Requirements For Biosimilars and Interchangeable Biological Drugs in the United States – in Plain Language* 45 DRUG INFO. J. 155, 157 (2011).

<sup>30</sup> FDA, *Biosimilars Frequently Asked Questions About Therapeutic Biological Products*, at [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologic Applications/ucm113522.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm).

<sup>31</sup> *Id.*

<sup>32</sup> *Id.*

<sup>33</sup> Preparing for Biosimilars, *supra* note 16.

<sup>34</sup> Lucio, *supra* note 11.

<sup>35</sup> Preparing for Biosimilars, *supra* note 16, at 3.

<sup>36</sup> FDA, *Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product* (April 2015) at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

with each phase of biosimilar approval meant to resolve any residual uncertainty from previous steps.<sup>37</sup>

A 351(k) application must include information demonstrating that the biological product is biosimilar to a reference product.<sup>38</sup> The sponsor must prove that the biosimilar utilizes the same mechanisms of action for the proposed conditions of use, that conditions of use proposed in labeling have been previously approved for the reference product, that it has the same route of administration, dosage form, and strength as the reference product, and is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent.<sup>39</sup>

As mentioned, the PHS Act requires that a 351(k) application include, among other things, information that demonstrates biosimilarity based upon the “totality of evidence.” This evidence is derived from three main sources: analytical studies demonstrating that the biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components; animal studies (including the assessment of toxicity); and a at least one clinical study that is sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.<sup>40</sup>

The BPCI Act also authorizes the FDA to designate certain biosimilars as “interchangeable,” meaning that a pharmacist could dispense the product in place of the originator without the involvement of the prescriber.<sup>41</sup> The FDA has stated that while it has authority to grant interchangeability status, it does not expect to make such a determination upon initial approval of the biosimilar.<sup>42</sup> Nevertheless, this subject has been contested in many settings, particularly in state legislatures across the country as will be discussed *infra*. Ultimately, each state’s pharmacy practice act will determine the process for implementing interchanges and substitutions. State laws are currently an area of active debate with regard to issues such as physician notification, patient consent, documentation, and record retention. For products designated by the FDA as

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<sup>37</sup> Lucio, *supra* note 11, at 1.

<sup>38</sup> Christl, *supra* note 21, at 9.

<sup>39</sup> *Id.*

<sup>40</sup> *Id.* at 10.

<sup>41</sup> Sensabaugh, *supra* note 25, at 3.

<sup>42</sup> FDA, *Draft Guidance for industry: Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009* (May 2015) at <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf>.

interchangeable with the originator product, determining best practices for substitution in the acute-care setting may be relatively straightforward, but their implementation in outpatient, specialty pharmacy, and retail environments may be much more complex.

*C. Exclusivity under the Biologics Price Competition and Innovation Act of 2009*

To address the uncertainty surrounding the approval pathway of biologics, Congress passed the Biologics Price Competition and Innovation Act of 2009 (BPCIA) as part of health care reform under the Patient Protection and Affordable Care Act. The BPCIA contains a 12-year exclusivity period for the innovator product during which time the FDA will not approve any “follow-on-biologic” that references the innovator product.<sup>43</sup> These exclusivity protections may actually be more useful to innovators than a patent because of the high level of legal uncertainty surrounding biologic patent law. To complicate things further, sponsors may not even be able to submit their applications to the FDA for at least four years after the innovator receives approval.<sup>44</sup>

Like the Hatch-Waxman act did for generic drugs, the BPCIA created a scheme for resolving challenges of patents for innovative biologics approved under the PHSA. This scheme is “designed to enable the resolution of patent disputes before a biosimilar enters the market.”<sup>45</sup> Under such a scheme, “the reference product sponsor and biosimilar applicant privately exchange information about relevant patents and negotiate to identify patents that will be litigated through an immediate litigation procedure.”<sup>46</sup>

However, unlike the Hatch-Waxman Act’s patent litigation scheme, the scheme created for biosimilars “includes no provision preventing FDA from approving a biosimilar if the biosimilar applicant indicates it will wait for patent expiry” before entering the market, “provides no stay of FDA approval of a biosimilar where a patent infringement suit has been brought,” and “provides no special incentive for biosimilar applicants to challenge or design around innovator patents.”<sup>47</sup>

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<sup>43</sup> 42 U.S.C.A. § 262(k)(7)(A) (2010).

<sup>44</sup> 42 U.S.C.A. § 262(k)(7)(B) (2010).

<sup>45</sup> Bogaert, et al., *Biosimilar regulation: important considerations and global developments*, PRACTICALLAW.COM (2011), at <https://www.practicallaw.com/3-500-9862>.

<sup>46</sup> *Id.*

<sup>47</sup> *Id.*

#### IV. LAWS OF THERAPEUTIC SUBSTITUTION

The practical and legal Pharmacists are given significant responsibility by both federal and state governments to help control drug costs by making effective generic-substitution choices. Pharmacists are uniquely positioned to leverage their skills and knowledge to into a value-based therapeutic decision, tailored to a patient's specific needs. Equally important is a pharmacist's unique ability to recognize when a generic substitution is not appropriate. Pharmacists should identify opportunities for physician consultation to achieve optimal treatment outcomes that balance demonstrated safety and cost considerations.

The FDA has taken much of the guesswork out of evaluating whether two drugs may be substituted for one another with publication of the *Orange Book*.<sup>48</sup> According to the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as *The Orange Book*, drug products must demonstrate pharmaceutical equivalence and bioequivalence to be considered therapeutic equivalents.<sup>49</sup> Therapeutic equivalent drugs are either A-rated (meaning that there are no known or suspected bioequivalence problems) or AB-rated (actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence).<sup>50</sup> A-rated drugs may be designated AA, AN, AO, AP, or AT, depending on the dosage form.<sup>51</sup> This rating is often the basis of state-specific substitution laws. In most states, pharmacists cannot substitute "nontherapeutic equivalent products" without first consulting the prescriber.<sup>52</sup> "Some states allow substitution between products as long as state-specific criteria are met, such as having the same active ingredient, dosage form, dose, and route of administration."<sup>53</sup>

For a number of years, before the discussion of biosimilars, at least 14 states and Puerto Rico have required pharmacists to substitute a generic version of the prescribed drug if all prescription requirements are met.

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<sup>48</sup> Jesse C. Vivian, *Generic Substitution Laws*, 33 U.S. PHARM. 30, n.6 (2008), <http://www.uspharmacist.com/content/s/44/c/9787/>.

<sup>49</sup> *Electronic Orange Book: Approved Products with Therapeutic Equivalence Evaluations*, 35th Edition, available at FDA.GOV, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

<sup>50</sup> *Id.* at xiii.

<sup>51</sup> *Id.*

<sup>52</sup> *State Regulations on Generic Substitution*, 22 PHARM. LETTER/PRESCRIB.220901, n.9 (Sept. 2006).

<sup>53</sup> *Id.*

These laws are not invalidated by biosimilar substitution measures enacted as of June 2014.<sup>54</sup>

*A. Federal Regulations Concerning Interchangeability of Biosimilars*

According to U.S.C. Section 262(k)(4) - Safety Standards For Determining Interchangeability:

Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that (A) the biological product (i) is biosimilar to the reference product; and (ii) can be expected to produce the same clinical result as the reference product in any given patient; and (B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

*B. Overview of State Legislation Concerning Interchangeability of Biosimilars*

As the FDA continues work on implementing the BPCI Act, states have considered proposals to restrict substitution of biologic medications. Currently, there is concern that traditional statutes regulating the substitution of traditional generic drugs may be misapplied to new biosimilars that are not identical to the originator. This has led many legislatures to amend older state laws, or add new sections, to address the medical and chemical characteristics of biologics and any future generic-style “follow-on” biologics, biosimilars, or interchangeable biological products.<sup>55</sup>

“In the past two years at least 31 states have considered legislation establishing state standards for substitution of a ‘biosimilar’ prescription

<sup>54</sup> Richard Cauchi, *supra* note 5. See generally NABP: 2014 Survey of Pharmacy Law, pp. 67-70. Available at [http://www.ncsl.org/documents/health/Biologics\\_BiosimilarsNCSLReport2015.pdf](http://www.ncsl.org/documents/health/Biologics_BiosimilarsNCSLReport2015.pdf).

<sup>55</sup> National Conference of State Legislatures, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars* (Jan. 2015), at [http://www.ncsl.org/documents/health/Biologics\\_BiosimilarsNCSLReport\\_July\\_2014.pdf](http://www.ncsl.org/documents/health/Biologics_BiosimilarsNCSLReport_July_2014.pdf).

product to replace an original biologic product.”<sup>56</sup> Key features of state legislation include: prevention by a prescriber of substitution with a biosimilar by writing “dispense as written” or “brand medically necessary”; consideration for substitution must first be approved as “interchangeable” by the U.S. Food and Drug Administration; notification of the prescriber of a substitution with a biosimilar; notification of or consent by the patient regarding the substitution; and recordkeeping of substituted biologics by both pharmacists and prescribers.<sup>57</sup> States will be required to maintain a public or web-based list of permissible interchangeable products.<sup>58</sup> In addition, some states require the pharmacist to explain the cost or price of the biologic and the interchangeable biosimilar and many provide immunity for pharmacists who make a substitution in compliance with biologics state law.<sup>59</sup> As of the end of 2014, eight states had enacted such statutes, and a number of other states had made unsuccessful attempts.<sup>60</sup>

Some states attempted to pass legislation that used different approaches such as “right-to-try” legislation, proposing to allow use of experimental drugs prior to full FDA approval and economic incentive measures intended to expand biologic research and manufacturing in individual states.<sup>61</sup> Supporters of state proposals believe the ultimate decision on substitution should be left to the patient’s prescribing physician. Opponents believe state proposals are restrictive and inconsistent with forthcoming national standards, and will increase the cost of healthcare.

## V. WHAT ROLE SHOULD STATE LAWS PLAY?

Not all health policy stakeholders agree on the role of state laws in regulating biological and biosimilar medications. The paragraphs that follow provide an overview of some of the considerations put forth by various interest groups that support, oppose, or criticize key features of state legislation.

### A. *Arguments for State Biosimilar Legislation*

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<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> *Id.*

<sup>59</sup> *Id.*

<sup>60</sup> *Id.* at 2.

<sup>61</sup> *Id.*

Biologic drug companies and some patient advocacy groups, whose views are often closely aligned with those of the drug industry, maintain that the FDA will develop appropriate standards for the approval of safe biosimilar and interchangeable biologic products. However, they also believe that additional protections are needed in state substitution policies that will “safeguard patient safety and the primacy of the physician-patient relationship,” and “ensure transparency and communication between patients and their treatment care teams.”<sup>62</sup>

Proponents of state legislation argue that states must step in to protect patients that could potentially be exposed to biosimilars without their knowledge or consent. They argue that states should develop new statutory protections for patients that provide physicians the authority to decide whether interchangeable biologics are appropriate substitutions for an originator product. Some proponents go so far as to argue that the FDA’s approach conflicts with the constitutional protections of trade secrets. They argue that the FDA’s approach conflicts with federal laws designed to ensure the safety of biologics, presenting serious safety concerns and that the duty falls to the states to enact proper legislation requiring prior authorization from a physician, and informed consent from the patient, before a pharmacist may substitute an biosimilar for an innovator product.

Biologic drug companies and other state biosimilar legislation supporters have also voiced concerns over quality and support the need for additional safeguards in state legislation.<sup>63</sup> For example, the trade organization that represents biologic drug companies argues, “Even though interchangeable biologics will be expected to produce the same clinical result, it remains the case that patients could react differently to an interchangeable biologic than if they were given the innovator product due to the complex nature of biologic products and how they work in the human body.”<sup>64</sup>

Supporters of state legislation have also raised concerns regarding adverse events, arguing that, “everyone should know which biologic a patient is taking so it can be used for adverse event reporting.”<sup>65</sup> Supporters of the notification provisions, including some patient advocacy

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<sup>62</sup> Purvis, *supra* note 21.

<sup>63</sup> *Id.* at 2.

<sup>64</sup> *Id.*

<sup>65</sup> *Id.*

groups and drug manufacturers, insist these provisions protect the patient-physician relationship and allow prescribers to monitor the patient's experience with the biosimilar.<sup>66</sup>

According to the Institute for Patient Access (IPA), "Biological medications differ substantially from conventional drugs and are classified differently by the FDA; as a result, laws and regulations developed for conventional drugs cannot be applied to biologics. Under current state laws, pharmacists may substitute conventional generic drugs for name-brands without notifying the physician."<sup>67</sup> The IPA asserts that, "even with therapeutically interchangeable biologics, underlying differences . . . may cause adverse events in some patients or may lead individual patients to respond better to one biologic than another," and emphasizes the importance of recordkeeping so that physicians can determine exactly which biologic was given to the patient.<sup>68</sup>

According to the Biotechnology Industry Organization (BIO), states laws that limit substitution "preserve patient access to accurate prescription information, maintain incentives for innovation, and promote a competitive market for biologic therapies."<sup>69</sup> The BIO advocates for "full transparency" in the substitution process as "patients and their physicians should have the right to know what biologic medicine the patient receives from the pharmacy."<sup>70</sup> The BIO asserts that state biosimilar legislation "properly addresses the need for physician communication and represents the interests of those who stand to benefit from this new cutting-edge technology."<sup>71</sup>

### *B. Arguments Against State Biosimilar Legislation*

In contrast, generic drug manufacturers, third party payers, and many consumer groups argue that recent state biosimilar substitution legislation is "designed to preemptively deter the substitution and use of biosimilars," which frustrates congressional intent to secure cost savings for consumers and taxpayers.<sup>72</sup> These groups rely on research that shows

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<sup>66</sup> Mark Lowry, *States Grappling With Biosimilar Substitution Laws*, Drug Topics: Voice of the Pharmacist, (Apr. 2, 2015) at <http://drugtopics.modernmedicine.com/drug-topics/news/states-grappling-biosimilar-substitution-laws?page=full>.

<sup>67</sup> National Conference of State Legislatures, *supra*, note 54.

<sup>68</sup> *Id.*

<sup>69</sup> *Id.*

<sup>70</sup> *Id.*

<sup>71</sup> *Id.*

<sup>72</sup> Purvis, *supra* note 21.

“states with patient consent requirements have generic substitution rates that are 25 percent lower than states that do not.”<sup>73</sup> In addition, some notification provisions effectively stifle competition, since the difficulty in contacting doctors and the time-consuming recordkeeping will discourage pharmacists from substituting less-expensive biosimilars for reference biologics.<sup>74</sup> An additional concern among those who oppose state biosimilar substitution legislation is that requiring pharmacists to inform patients and obtain the prescriber’s consent to substitute will exacerbate any lingering anxiety and suspicion of generic alternatives, which will likely deter biosimilar use.<sup>75</sup>

Opponents also argue that state biosimilar legislation is “extremely premature given that the FDA is still in the process of refining the biosimilar approval pathway, and that implementing state legislation at such an early stage could result in unnecessary conflict between state and national laws.”<sup>76</sup> Specifically, opponents are concerned that state legislation could conflict with federal laws that allow substitution for biosimilars that are considered “interchangeable” with their innovator counterpart without the involvement of the prescribing doctor. “The FDA has also expressed concerns about the effects of state biosimilar substitution legislation on access to lower-cost treatments.”<sup>77</sup>

According to America’s Health Insurance Plans (AHIP), an effort should be made to “remove barriers at the state level that restrict the use of biosimilars.”<sup>78</sup> AHIP emphasizes that some states have already adopted legislation that may restrict the availability of biosimilars before they even reach the market, and expresses concern that these proposals “will limit patient access to drugs that are not clinically different, yet cost substantially less than their brand-name counterparts.”<sup>79</sup>

The Governor of California stated his support for a state bill that would “allow interchangeable biosimilar drugs to be substituted for biologic drugs, once approved by the FDA.”<sup>80</sup> However, the bill would have required pharmacists to notify prescribers about which drug was dispensed.<sup>81</sup> The Governor noted that, while doctors may welcome this

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<sup>73</sup> *Id.*

<sup>74</sup> Lowry, *supra* note 58.

<sup>75</sup> Purvis, *supra* note 21.

<sup>76</sup> *Id.*

<sup>77</sup> *Id.*

<sup>78</sup> Richard Cauchi, *supra* note 5.

<sup>79</sup> *Id.*

<sup>80</sup> *Id.*

<sup>81</sup> *Id.*

information, there remained a significant concern that the requirement itself would cast doubt on the safety and desirability of more cost-effective alternatives to biologics.<sup>82</sup>

It may come as little surprise that attempts by state legislatures to erect barriers to generic substitution have been met with firm opposition from the Generic Pharmaceutical Association (GPhA). The GPhA maintains that, “Interchangeability or substitution is the engine that drives generic competition. It is the reason why generic drugs have generated savings of \$1.06 trillion over the past decade. The way that FDA deals with interchangeability will be directly responsible for the market dynamics generated by the biosimilar pathway.”<sup>83</sup> The GPhA strongly supports automatic substitution legislation that “allows interchangeable biologics to be automatically substituted at the pharmacy; upholds the current pharmacy practice of automatic substitution; insists on the science-based FDA determination of interchangeability; and treats all interchangeables and their corresponding brand biologics the same once an interchangeable is approved.”<sup>84</sup> The GPhA supports legislation that creates a competitive market for biosimilar products and provides patient access to affordable versions of these critical medicines.

## VI. IMPLICATIONS OF BIOSILIMAR LEGISLATION

State biosimilar legislation will have profound effects on many aspects of healthcare. There are many rational reasons to support legislation that preserves the patient-physician relationship, requires diligent record keeping, and respects a patient’s autonomy in choosing his or her own treatment plan. However, if states enact legislation that aggressively discourages substitution, there will be a pronounced reduction in market competition, and a consequent increase in price. Alternatively, if states enact legislation that fails to provide sufficient stability in a new and unpredictable market, pharmaceutical companies will struggle to realize a return on their investment, which will discourage innovation. If legislatures fail to protect these investments, innovators will be less likely to develop new products to treat challenging diseases. The ability of state legislatures to successfully balance the interests of innovation and access will have profound impacts on the future sustainability of the

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<sup>82</sup> *Id.*

<sup>83</sup> *Id.*

<sup>84</sup> *Id.*

pharmaceutical industry and the provision of healthcare.

*A. Effects on the Provision of Healthcare*

State legislation will undoubtedly have significant impacts on the availability and delivery of biologics. Regardless of the challenges that may exist when selecting a biologic product or a biosimilar counterpart, there are a number of considerations that should be evaluated by healthcare providers in order to maximize the value and quality of the products and service they deliver. Physicians, pharmacists, and all members of the healthcare team should work together to implement evidence-based medicine into formulary with the use of approved biologics and biosimilars in appropriate circumstances.

*1. Formulary Management of Biosimilars*

While biosimilars may be relatively new, effective formulary management techniques have been around for decades.<sup>85</sup> Most organizations are familiar with therapeutic interchange protocols for both traditional and biologic drugs. The concept, competencies, and infrastructure already exist for the successful formulary management of biosimilars.<sup>86</sup> Health systems should continue to utilize existing processes to evaluate biosimilars for formulary inclusion, carefully consider scope of indications for use, and conduct economic analysis, considering costs, reimbursement, and patient impact.

Generally, the costs of generic drugs are substantially less than their brand-name counterparts. The same has yet to be seen with biosimilars because of limited market competition. “While generic medications typically cost about 80% less than brand-name drugs, the savings realized by adding biosimilars to formulary may be less substantial.”<sup>87</sup> Biosimilars are expected to cost only about 20 to 30 percent less than the originator product.<sup>88</sup> Although the savings compared to traditional small molecule drugs are seemingly less significant, biosimilars have the potential to generate considerable savings and should be thoroughly

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<sup>85</sup> B. Hawkins, *Principles of a Sound Formulary System. Best Practices For Hospital & Health-System Pharmacy: Positions and Guidance Documents of ASHP*. American Society of Health-System Pharmacists; 2006:110-113.

<sup>86</sup> *Id.*

<sup>87</sup> Lucio, *supra* note 11.

<sup>88</sup> *Id.*

evaluated for formulary inclusion.

## 2. *Pharmacovigilance and Postmarketing Surveillance*

Postmarketing surveillance will likely be a major responsibility for pharmacists and practicing clinicians to identify and report potential safety and immunogenicity information. Pharmacovigilance activities are essential to assess the ongoing safety and immunogenicity concerns associated with the use of biologics. “Because biologic products . . . are by their very nature capable of eliciting immune responses in humans, immunogenicity is a focus of safety assessments during development.”<sup>89</sup> “The goal of the immunogenicity assessment is to evaluate potential differences between the biosimilar and the reference product in the incidence and impact of the human immune response.”<sup>90</sup> Post-approval data collection on safety data for these drugs is important because there is a limited clinical database at the time of a biosimilar’s approval.<sup>91</sup>

Another important aspect of post-approval data collection is that the data allows researchers to distinguish between different biosimilar products and the reference products, making it possible to ascertain which specific product a patient has received. “Because of the potential risks associated with biopharmaceuticals, particularly immunogenicity, and the potential for clinically meaningful differences between products, there is a need for rigorous pharmacovigilance programs to monitor all biopharmaceuticals for safety and efficacy issues during the post-approval period.”<sup>92</sup> Manufacturers of biosimilars are required to implement adequate postmarketing surveillance mechanisms “to differentiate between the adverse events associated with the proposed product and those associated with the reference product, including the identification of adverse events associated with the proposed product that have not been previously associated with the reference product.” The FDA may also require “a postmarketing study to evaluate certain safety risks.”<sup>93</sup>

<sup>89</sup> Walter Reinisch, MD & Josef Smolen, MD, *Biosimilar Safety Factors in Clinical Practice*, 44 *Seminars in Arthritis and Rheumatism*, S9, S10 (2015) at <http://dj.sagepub.com/content/45/2/155.full.pdf+html>.

<sup>90</sup> *Id.* at 12.

<sup>91</sup> H. Mellstedt et al., *The Challenge of Biosimilars*, 19 *ANNALS OF ONCOLOGY* 411, 415 (2007).

<sup>92</sup> *Id.* at 415-16. *Noting*, because of the potential risks associated with biopharmaceuticals, particularly immunogenicity, and the potential for clinically meaningful differences between products, there is a need for rigorous pharmacovigilance programs to monitor all biopharmaceuticals for safety and efficacy issues during the post-approval period.

<sup>93</sup> Lisa A. Haile & Kimberly K. Egan, *Regulations for Biosimilars. As biologic drug patents begin to expire, generic versions will hit the market—but how will they be regulated?* (June 1, 2012) at <http://www.the-scientist.com/?articles.view/articleNo/32152/title/Regulations-for-Biosimilars/>.

Pharmacists should leverage their unique position in the healthcare delivery chain to participate in postmarketing surveillance. Pharmacists are one of the most accessible healthcare providers for patients to contact with concerns regarding safety and efficacy of biologics. Furthermore, pharmacists have access to extensive databases and can utilize existing systems to ensure adequate recordkeeping and adverse event reporting.

*B. Effects on the Pharmaceutical Industry*

An additional obstacle for biosimilars involves the particular manner in which patents are litigated.<sup>94</sup> “Biosimilar legislation provides a highly specific process for the identification and negotiation of patents between the innovator and the biosimilar applicant.”<sup>95</sup> The 351(k) pathway likely will be the avenue for most biosimilar approvals. The process requires that a biosimilar sponsor disclose to an innovator critical information such as its biologics license application and manufacturing process.<sup>96</sup> However litigation challenges could drive competitors to expedite their entry into the market.<sup>97</sup>

“Substantial uncertainty remains as to whether biosimilar applicants would be willing to disclose this information and if the negotiation of patents can take place within the time frame described by the legislation.”<sup>98</sup> Regulatory uncertainty has increased the level of risk in the market, which has increased the cost of entry, and resulted in fewer firms willing to enter the biosimilar market. This is especially problematic for smaller biotechnology companies whose investments in new biologics expose them to serious financial risks. If courts and policymakers fail to protect these investments, innovators will be less likely to develop new products to treat challenging diseases. Uncertainties over the impending regulatory framework and defense strategies by name brand biologic manufacturers have caused delays in biosimilar development.

The FDA should focus on setting guidelines so that more biosimilar firms can enter the market. There is always a lag between application and the regulatory decision concerning approval. It is during this time that the FDA can resolve other issues that have arisen, such as naming and state substitution laws. It is important for the FDA to establish definitive

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<sup>94</sup> Preparing for Biosimilars, *supra* note 16, at 6.

<sup>95</sup> *Id.*

<sup>96</sup> *Id.*

<sup>97</sup> Lucio, *supra* note 11.

<sup>98</sup> Preparing for Biosimilars, *supra* note 16.

guidelines to minimize uncertainty so that firms will understand the process to be undertaken. Only then can biosimilar competition provide the desired benefit to consumers through access to lower priced alternative therapies that will allow patients to achieve better medical outcomes.<sup>99</sup>

Notwithstanding the significant potential for biosimilars, their establishment in the US market will likely be a slow process. Stringent clinical requirements and a complicated procedure for resolving patent disputes are likely to delay market uptake. Originator patents usually have multiple lines of defense, including process patents, which may also slow the entry of biosimilars when new markets become available. Given the highly technical issues involved and the lack legal precedent, it is difficult to predict how successful the biosimilar market will be in the coming years.

It will take time for the FDA to believe in the industry's ability to safely and consistently reproduce these complex molecules and for physicians overcome their concerns over safety and efficacy. The financial motivation for both payers and patients will also be crucial. However, even if regulatory barriers hinder biosimilars initially, the financial incentives will ultimately drive acceptance of biosimilar long-term as entry of leading US companies foster the sector's credibility. A number of factors will impact the opportunities for cost saving in the US including ease of access in the short term, speed of uptake, clarity of regulation and, the role of public and private stakeholders.

The market exclusivity for the top ten best-selling originator biologics is set to expire between now and 2019, and current estimates suggest that by 2024, the savings from biosimilars in the US could reach \$250 billion. Despite the lingering concerns regarding the safety and reproducibility of biosimilars, the market for biosimilars is expected to experience significant growth in the coming years, being driven by the extensive pipeline and the number of companies becoming involved in this area, including some large pharmaceutical companies who are developing biosimilar versions of competitor products in order to ensure they are able to compete at all levels.

Some of the most promising biosimilars in the US include Avastin, Epogen, Herceptin, Humira, Intron A, Neulasta, Neupogen, Pegintron, Procrit, Remicade, and Rituxin. In July 2014, the FDA accepted a BLA from Sandoz for (Zarxio) filgrastim, as a biosimilar to the reference

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<sup>99</sup> Joseph P. Fuhr, *Biosimilars Can Save Lives and Cost Less*, FORBES (Aug. 8, 2014), available at <http://onforb.es/1ydiWtj>.

biologic Neupogen.<sup>100</sup> In August 2014, Celltrion filed a BLA for infliximab (Remsima) as a biosimilar to the reference biologic Remicade.<sup>101</sup> The FDA recently gave tentative approval to Eli Lilly's "biosimilar" insulin glargine (Basaglar), but will not be available until the company resolves patent litigation with Sanofi.<sup>102</sup>

The EU has been dealing with biosimilars since 2006. The most common of which include Omnitrope, Binocrit, Abseamed, Silapo, Retacrit, TevaGastrim, Ratiogastrim, Biograstim, and Zarzio.<sup>103</sup> Although the EU has established and maintained a seemingly functional system of approval and regulation for biosimilars, common issues remain to be resolved regarding substitutability and interchangeability. Given that the European system has grappled with many of the same issues as the US concerning substitutability, interchangeability, and nomenclature, it is apparent that the US is not alone in its struggle to implement a cohesive system of approval and regulation.

## VII. RECOMMENDATIONS

Biosimilars are becoming a significant portion of our national healthcare spending. Every effort should be made by healthcare professionals to remain cost conscious, while maintaining a high level of patient care in all settings. Biosimilars present unique opportunities and responsibilities for physicians and pharmacists alike. Physicians should educate themselves about the biologic approval process and remain mindful that many biosimilars are approved for only a subset of the indications of its reference biologic. Physicians should work as a part of the P&T committee, using established evidence-based processes in the evaluation of medications for formulary consideration. They should communicate with patients and pharmacists regarding the goals of therapy and clearly indicate the permissibility of substitution.

Pharmacists should also act as leaders in the objective evaluation of

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<sup>100</sup> Sandoz Media Center, *FDA Accepts Sandoz Application for Biosimilar Filgrastim*, (July 24, 2014), at <https://www.novartis.com/news/media-releases/fda-accepts-sandoz-application-biosimilar-filgrastim>.

<sup>101</sup> Celltrion: What's New, *Celltrion Files for US FDA Approval of Remsima*, (Aug. 11, 2014), at [http://www.celltrion.com/en/company/notice\\_view.asp?idx=456&code=ennews&intNowPage=1&menu\\_num=&align\\_year=all](http://www.celltrion.com/en/company/notice_view.asp?idx=456&code=ennews&intNowPage=1&menu_num=&align_year=all).

<sup>102</sup> Jean-Marc Guettier, MD, Department of Health and Human Services, *Tentative Approval*, (2014), at [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2014/205692Orig1s000TAltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205692Orig1s000TAltr.pdf)

<sup>103</sup> Generics and Biosimilars Initiative, *Biosimilars Approved in Europe*, (last updated Feb. 27, 2015), at <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe>.

biosimilars using existing formulary processes. They should identify safety and immunogenicity risks and evaluate such risks with respect to cost containment considerations. Pharmacists should be key players in pharmacovigilance and leverage their accessibility to patients as well as their access to databases and existing recordkeeping capabilities as a conduit of information for government agencies and manufacturers.

Given the complexity of biosimilars, greater scrutiny will be required of P&T committees than what is traditionally devoted to the review of generic medications.<sup>104</sup> “P&T committees should use a structured, evidence-based process in the evaluation of medications for formulary consideration.”<sup>105</sup> Brand name products should be when used only when indicated and pharmacists should utilize substitution for approved interchangeable products under the same principles of existing pharmacy law.

Products should only be considered for therapeutic interchange when there is evidence of therapeutic equivalence, comparable safety profiles, significant cost advantages, a clear interchange process, an ability to “opt out” in specific circumstances, and an ability to assess outcomes.<sup>106</sup> Although pharmacists can use discretion to substitute interchangeable products, they are not only allowed, but are expected to utilize generics absent instructions to the contrary. Decisions should be founded on the evidence-based clinical, ethical, legal, social, philosophical, quality-of-life, safety, and economic factors that result in optimal patient care.<sup>107</sup> Pharmacists should make a concerted effort to counsel patients on the risks and benefits of a given biologic product and should proactively communicate with physicians when substitutions are appropriate.<sup>108</sup> The process of evaluating biosimilars must include physicians, pharmacists, and other appropriate health care professionals. The process should be evidence-based and should not be based solely on economic factors.

Regarding payment, insurance companies should be expected to charge increased rates when patients choose the brand name without documented medical necessity. Insurance plans will likely use established formulary-review processes to review each drug on its own merit. If two drugs are considered “therapeutically equivalent,” then the plan will

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<sup>104</sup> Lucio, *supra* note 11.

<sup>105</sup> American Society of Health-System Pharmacists, *ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System*, *AM J HEALTH-SYS PHARM*, 65:1272–83 (2008).

<sup>106</sup> Stevenson, *supra* note 9.

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

decide where on its benefit tier each drug should reside or if it should be covered at all. Plans are likely to use patient financial incentives to drive the use of biosimilars. Insurance companies should implement policies that encourage biosimilar utilization, either through prior-authorization requirements, or through tiered payment structures that shift a portion of the cost of the brand name product back to the patient unless the branded product is considered to be medically necessary by the prescriber.

State laws should recognize that physicians should have the ability to indicate that a patient is not a candidate for generic substitution or interchange. While mandatory notice and pre-approval provisions are unnecessary for interchangeable products, physicians should be able to prevent substitution when it is determined to be medically necessary. Pharmacists should only be permitted to make substitutions for products that are approved as “interchangeable.” Although the pharmacist can play a key role in patient education, risk management, and adverse event reporting, the prescribing physician is in the best position to evaluate a patient’s initial treatment options and must be given a reliable way to ensure that the patient receives the precise medication that the prescriber intends. Therefore, even if states do not require pre-authorization, physicians must be able to mandate the dispensation of the desired product by writing the phrases “dispense as written” or “brand medically necessary” on the prescription in order to control the dispensation of a brand name product when substitution would be inappropriate. However, as with therapeutic substitutions of traditional small molecule drugs, in the absence of an indication to the contrary, pharmacists should be expected to utilize the most cost effective treatment available. If a biologic product has been approved to be “interchangeable,” it should generally be substituted unless the prescriber has indicated that such substitution is impermissible.

An effort must be made to reconcile biosimilar substitution laws with existing state laws on generic substitution. Existing substitutions laws provide clear and concise rules that enable a physician to prescribe a medication with knowledge that the pharmacist will attempt to utilize the most economical treatment for the patient. Physicians are familiar with the practice of substitution and are provided with various ways to indicate when substitution is impermissible. In the event that a patient requires a specific biologic, physicians can use existing practices to indicate when a particular product should be utilized. State laws should recognize that the treatment process involves a number of healthcare providers and should enable each provider to contribute to the safe and effective delivery of

cost-effective healthcare.

### VIII. CONCLUSION

Biosimilars present significant challenges and opportunities for healthcare providers who manage formularies and develop strategies for patient care. It is important to engage in a cost-benefit analysis to examine the true impact on patient welfare. Existing principles of formulary management that are currently employed for traditional small molecule drugs should be applied to biosimilars. Pharmacists and other healthcare providers must educate themselves and be prepared to play leadership roles in the safe and appropriate introduction of biosimilars into health systems. Healthcare providers should increase their understanding of the regulatory pathway for biosimilars, the likely targets for biosimilar development, and the clinical communications that will need to occur to support appropriate use.

Federal legislation has successfully implemented a number of cost saving measures designed reduce overall spending on healthcare without stifling the development of new medication. State laws should embrace these cost saving measures and should work alongside federal legislation to address the concerns of quality and safety without sacrificing dedication to cost containment. As the market for biologics continues to grow, it will become increasingly important for state legislation to balance the competing interests of scientific innovation and public access. With proper education and the implementation of state laws that support the optimal utilization of biosimilars, the US system will be one step closer to affordable healthcare.



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