Naming Biosimilars: The Debate and Its Public Health Implications

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The enactment of the Biologics Price Competition and Innovation Act (BPCIA)\(^1\) in March 2010 as part of health care reform marked a watershed event in the regulation of biologic drugs in the United States. Representing the culmination of years of stakeholder discussion and negotiation, the BPCIA created an abbreviated regulatory

pathway for the licensure of “biosimilars.” This new category of biologics may be licensed on the basis of a comparison against an innovative “reference” biologic and more-limited clinical (and possibly other) data than would be required for approval under the standard pathway.²

Now, four years after enactment of the BPCIA, stakeholders continue to debate numerous issues related to its implementation. Although the U.S. Food and Drug Administration (FDA) has not yet licensed any biosimilars or acknowledged that it has received any biosimilar applications, the agency is expected to begin licensing biosimilars soon. And before it does, the agency must confront—and finally resolve—an issue that has been contentious since the earliest discussions of biosimilar legislation: whether biosimilars should have the same nonproprietary names as those of their reference products. The impact of FDA’s decision will extend beyond the names of biosimilars themselves, affecting biologic prescribing, dispensing, and safety monitoring.

Origins of the Debate

The Biosimilar Approval Pathway

Congress intended for the BPCIA to promote the development of lower-cost biologic therapies while maintaining incentives for manufacturers to develop novel biologic therapies. These goals and the law’s design are similar in concept to those of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, which established a pathway for the approval of generic drugs.

The BPCIA recognizes that in critical respects, however, biosimilars are not like generics. The law requires a biosimilar applicant to demonstrate that its proposed biosimilar is “highly similar” to the reference product and that there are “no clinically meaningful differences” between the two products.³ Applicants must submit analytical studies, animal studies, and a clinical study or studies (unless any of these

² Compare Public Health Service Act (PHSA) § 351(k) (biosimilar pathway) with § 351(a) (standard approval pathway).
³ PHSA § 351(i)(2).
requirements is waived by the Secretary of the U.S. Department of Health & Human Services) to support licensure. A generic drug applicant, in contrast, must show that its product has the “same” active ingredient as the reference product and submit data demonstrating only that the two products are bioequivalent.

The different approval requirements for biosimilars and generics reflect the fact that unlike most chemically synthesized drugs, biologics are derived from living organisms and have much more complex molecular structures. Also unlike most chemically synthesized drugs, biologics are highly sensitive to their manufacturing processes. Even small changes in a manufacturing step have been known to result in meaningful changes to a biologic’s safety or effectiveness. In addition, given limitations in analytical technology it is currently not possible to demonstrate that two biologics manufactured by different companies using different starting materials and processes are structurally identical. Postmarket experience thus may reveal unexpected clinical differences between the two products that were not detected prior to approval. Products also may become less similar over time due to intentional or inadvertent changes to one or both products. In other words, even if two biologics are highly similar at a given point in time, slight changes to the manufacturing process of either one could cause them to diverge. These features of biologics pose challenges for prescribing, dispensing, and postmarket safety monitoring that will only grow as biosimilars enter the market.

The Need for a Naming Scheme

By federal law, every drug (including biologic) must have a nonproprietary name (e.g., “acetaminophen” or “insulin recombinant human”). Generics have nonproprietary names that are the same as those of their reference products. Because the active ingredients of biosimilars and their reference products are not identical and the quality and clinical profiles of a biologic may change over time, some stakeholders have argued

4 PHSA § 351(k)(2)(A).
6 Federal law requires every drug to include a nonproprietary name on its label. FDCA § 502(e)(1)(A); PHSA § 351(a)(1)(B)(i).
that a new naming paradigm is appropriate for biosimilars: biosimilars should receive nonproprietary names that are similar to, yet distinguishable from, those of their reference products.

Although lawmakers and stakeholders debated biosimilar naming during legislative negotiations, naming provisions were not included in the final law. Congress thus left biosimilars subject to the existing statutory provisions on drug names. Under the Federal Food, Drug, and Cosmetic Act (FDCA), a product’s nonproprietary name is: (1) the official name designated by FDA (under Section 508 of the FDCA);7 or, if FDA has not exercised its statutory naming authority; (2) the official title of the drug in an official compendium; or, if neither of the above; (3) the “common or usual name” of the drug.8

Shortly after enactment of the BPCIA, FDA signaled that it would issue a policy on biosimilar naming.9 But the agency has not yet done so. And with each passing year the issue becomes more pressing. The spotlight on naming has grown more intense, especially during the past six months, following the filing of two citizen petitions (by the Generic Pharmaceutical Association10 and Novartis11) formally asking FDA to require biosimilars to have the same nonproprietary names as their reference products. These petitions sparked support and criticism from other stakeholders, and were followed by the filing of a citizen petition (by Johnson & Johnson12) formally asking FDA to require biosimilars to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars. The Federal Trade Commission then

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7 Section 508 provides that FDA “may designate an official name” for any drug if it determines that such action is “necessary or desirable in the interest of usefulness and simplicity.” FDCA § 508(a).
8 FDCA § 502(e)(3).
10 Docket No. FDA-2013-P-1153 (petition dated Sept. 17, 2013). The Generic Pharmaceutical Association later informed FDA at a meeting in January 2014 that, although it continues to maintain the position taken in its citizen petition, it is considering supporting a proposal to require the nonproprietary names of biologics to include as a suffix—after the international nonproprietary name (INN)—the name of the particular manufacturer. FDA Meeting Minutes (Jan. 9, 2014), Docket No. FDA-2013-P-1153.
solicited comments as part of a workshop on February 4, 2014 that addressed (among other things) the competitive effects of biosimilar naming proposals.

**International Approaches to Biosimilar Naming**

With the enactment of the BPCIA, the United States joined more than a dozen other jurisdictions that already had adopted rules specific to the approval of biosimilars. Of those, Japan has implemented a requirement for, and Australia has proposed requiring, distinguishable names for all biosimilars. The European Union and other jurisdictions, in contrast, have tended to adopt the international nonproprietary names (INN) designated by the World Health Organization (WHO) as the name of a biosimilar. The INNs of biosimilars have traditionally (though not always) been the same as the INNs of the reference products.

This table summarizes the current biosimilar naming rules and practices in a number of jurisdictions.

<table>
<thead>
<tr>
<th>Country</th>
<th>Names of Biosimilars</th>
<th>Proprietary Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Nonproprietary Name</strong></td>
<td><strong>Proprietary Name</strong></td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td>The reference product Australian Biological Name (ABN) plus a “biosimilar identifier” (consisting of the prefix “sim” and a unique three letter code)</td>
<td>Permitted (no feature identifying product as a biosimilar required)</td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td>Brazilian Common Denomination (DCB) (i.e., the same as or similar to the INN, in practice before 2012 and by law since 2012), or in the absence of a DCB, the INN or Chemical Abstracts Service name</td>
<td>Permitted (no feature identifying product as a biosimilar required)</td>
</tr>
<tr>
<td>Country</td>
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</tr>
<tr>
<td></td>
<td><strong>Nonproprietary Name</strong></td>
<td><strong>Proprietary Name</strong></td>
</tr>
<tr>
<td>China</td>
<td>INN; if no INN exists, a manufacturer can apply to the regulatory authority for a nonproprietary name</td>
<td>Not permitted</td>
</tr>
<tr>
<td>Colombia</td>
<td>INN</td>
<td>Permitted (no feature identifying product as a biosimilar required)</td>
</tr>
<tr>
<td>Japan</td>
<td>Japan Accepted Name (JAN) (i.e., the INN possibly with slight modifications, if an INN exists) of the reference product + &quot;[&quot; + JAN of the reference product minus “rDNA,” if any + “Biosimilar” + the order number of the biosimilar product + &quot;]&quot;</td>
<td>JAN of the reference product without “rDNA,” if any + “BS” + dosage form + strength + company name (the company name may be in brackets if it would otherwise be confusing)</td>
</tr>
<tr>
<td>Mexico</td>
<td>INN</td>
<td>Permitted (no feature identifying product as a biosimilar required)</td>
</tr>
<tr>
<td>Russia</td>
<td>INN</td>
<td>Permitted (no feature identifying</td>
</tr>
</tbody>
</table>
For more than a year, however, WHO has explored developing a policy of assigning distinguishable names to all biosimilars.\textsuperscript{13} WHO has stated that if it maintained its current policy, the use of identical nonproprietary names could (among other things) lead to “inadvertent switching” of patients from one biosimilar to another.\textsuperscript{14} A WHO official thus indicated in 2012 that WHO’s current naming policy “is not satisfactory.”\textsuperscript{15} And at a meeting in October 2013, WHO announced that the INN Secretariat is in the “embryonic” stages of developing a scheme that would add a unique “biosimilar qualifier” to the INNs of biosimilars.\textsuperscript{16} If WHO adopted such a scheme, it would help facilitate a harmonized, global approach toward distinguishable names for biosimilars.


\textsuperscript{15} Id. at 4.

Public Health Implications

Stakeholders on both sides of the debate agree that any naming policy for biosimilars in the United States will have important implications for the prescribing, dispensing, and tracking of biologics. Some believe identical names will not impede effective pharmacovigilance (i.e., the postmarket monitoring of a drug’s safety), will reduce confusion and help prevent prescribing or dispensing errors, and will enhance patient access. Others have argued the opposite: distinct names are essential for pharmacovigilance in the upcoming era of numerous multi-source biologics, will better promote transparency and minimize prescribing or dispensing errors, and will not limit patient access.

Pharmacovigilance

Spontaneous adverse event reporting by physicians, patients, caregivers, and drug manufacturers is one of the primary ways in which a drug’s safety is monitored after marketing approval. Identifying the particular product associated with an adverse event can expand understanding of that product’s safety and efficacy profile, increase the likelihood of discovering an unexpected safety concern related to an individual product, and aid investigation into the root cause of quality or other issues associated with a product.

Some stakeholders have argued that distinguishable names will help manufacturers and regulators identify the particular biologic associated with an adverse event because the nonproprietary name is often the only product-specific information included in a spontaneous adverse event report. According to others, a product’s nonproprietary name is not designed to facilitate pharmacovigilance; it should be selected solely based on characteristics of the active ingredient. Some also have asserted that alternative methods for tracking biologics postmarket can better ensure effective pharmacovigilance.
Alternative methods for promoting pharmacovigilance, and their key limitations, include:

**Proprietary Name**

- Pros: It is expected that, unlike generics, most (if not all) biosimilars will be marketed with proprietary names. Inclusion of proprietary names in spontaneous adverse event reports would tie reports to specific products. Evidence suggests that adverse events associated with biosimilars have been successfully tracked by proprietary name in Europe.\(^{17}\)

- Cons: The FDCA does not require drugs (including biologics) to have proprietary names, so some biosimilar manufacturers may elect to not use them. Many adverse event reports omit the proprietary name in practice, and evidence suggests that adverse event reporters often incorrectly attribute adverse events to branded reference products when generic drugs with the same nonproprietary name were likely responsible.\(^{18}\) This can result in the pooling of data and an inability to identify the specific product associated with reported adverse events.

**National Drug Code Number**

- Pros: A National Drug Code (NDC) number is a three-segment, ten-digit number (that refers to the labeler, product, and trade package size) that uniquely identifies each drug. Inclusion of NDC numbers in spontaneous adverse event reports would tie reports to specific products. The NDC number also would convey more information (such as package size) than a distinguishable nonproprietary name.

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• Cons: Adverse event reports rarely include NDC numbers.\(^{19}\) These numbers may not be available to adverse event reporters, since they are not commonly used in hospitals (where many biologics are prescribed and administered) and may not appear on the labels of dispensed products. Given their length, NDC numbers are not easy to remember and could be recorded incorrectly on reports. And NDC numbers are not used in other countries, which could complicate aggregating adverse event data globally.

*Lot or Batch Number*

• Pros: Inclusion of product lot and/or batch numbers in spontaneous adverse event reports would tie reports to specific products. Unlike nonproprietary names, lot or batch numbers would help identify when the administered product was manufactured, assisting investigations into the root causes of unexpected adverse events or quality concerns.

• Cons: Spontaneous adverse event reports rarely include lot or batch information.\(^{20}\) These numbers are not easy to remember and patients and prescribers can identify the number only if they have not yet discarded the containers on which the information is printed. Further, lot and batch numbers still must be accompanied by other product-identifying information, such as product name or manufacturer name, to help timely identify the specific product associated with a reported adverse event.

*Manufacturer Name*

• Pros: Inclusion of the names of product manufacturers in spontaneous adverse event reports would tie reports to specific products.

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\(^{19}\) Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research, FDA Transcript, FDA Part 15 hearing Docket No. FDA-2010-N-0477 (Nov. 2, 2010) at 169; Lietzan, et al., *supra* note 18, at 6 (finding that NDC numbers are included in less than 0.01% of all adverse event records in the FAERS database).

Cons: Manufacturers (that receive adverse event information directly from physicians, patients, and caregivers) submit the majority of spontaneous adverse event reports to FDA. The manufacturer name associated with such a report is merely the name of the manufacturer submitting the report, and as previously noted, evidence suggests that physicians and patients often attribute adverse events to the incorrect product when products share the same nonproprietary name. In those cases, the reported manufacturer name is inaccurate.

Track and Trace Product Identifier

Pros: A law enacted in November 2013, the Drug Supply Chain Security Act (Title II of the Drug Quality and Security Act), requires drugs (including biologics) to be tracked throughout the supply chain using a unique product identifier. The product identifier includes a 20-digit code that in turn includes the NDC number, lot number, and expiration date of the product. Inclusion of this identifier in spontaneous adverse event reports would tie reports to specific products. Compared with a nonproprietary name, a product identifier would provide much more information about the particular product associated with an adverse event.

Cons: Adverse event reporters often will not know a biologic’s product identifier because the law does not require this information to be given to prescribers or patients. And like NDC numbers, product identifier numbers included in adverse event reports could be remembered or written incorrectly, given their length.

Prescribing and Dispensing Errors

The nonproprietary names of biosimilars may affect prescribing and dispensing practices. Prescribers may not realize that biologics with distinguishable nonproprietary names are highly similar, leading to accidental double dosing, according to stakeholders who favor identical names. Pharmacists also might confuse one distinct-yet-related name for another that looks and sounds similar, resulting in medication errors. In

21 Lietzan, et al., supra note 18, at 11.
contrast, others have argued that distinct-yet-related names would communicate similarity between products, safeguarding against double dosing. Distinguishable names also might minimize the risk of inadvertent switching between or among biologics when a physician prescribes by nonproprietary name.²²

**Patient Access**

Some stakeholders have questioned whether distinguishable names will stifle the uptake of biosimilars, needlessly limiting patient access to these lower-cost medicines. They have argued that prescribers, patients, and pharmacists may find distinguishable names confusing, given that generic drugs have the same names as their reference products. Distinguishable names also might suggest that biosimilars have clinical differences from their reference products, even though FDA must determine that there are “no clinically meaningful differences” between the products at the time of biosimilar licensure.²³

Others have argued that assigning biosimilar names that are distinct from, yet similar to, those of their reference products will reduce confusion by conveying that certain biologics are related, but not the same. In addition, identical names could incorrectly suggest that two biosimilars that share the same reference product (and therefore have the same name) have no clinically meaningful differences; the BPCIA requires no demonstration of similarity or other comparison between or among biosimilars. Stakeholders also have asserted that distinguishable-yet-related names may promote patient access by helping prescribers identify the biosimilars with the same reference product and available for prescribing. And by facilitating identification of the specific product responsible for unexpected adverse events, distinguishable names could reduce the potential for unnecessary recalls or warnings across an entire product class when a safety concern is limited to one product.

²² If a physician prescribed a product by nonproprietary name (out of habit or without realizing that another product shared that name), a pharmacy may dispense any product with that name, even if it is not the product the physician intended the patient to receive.
²³ PHSA § 351(i)(2)(B).
Conclusion

In light of the BPCIA’s silence on naming and with the first biosimilar approval on the horizon, FDA must announce how it will resolve the naming debate. It must consider the implications for patient welfare as it develops what stakeholders hope will be a sound and durable policy for this new category of biologics.