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FEATURES

The growing role of biologics and biosimilars in the United States: Perspectives from the APhA Biologics and Biosimilars Stakeholder Conference

Judy Crespi-Lofton, Jann B. Skelton*

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ABSTRACT

Objectives: The American Pharmacists Association (APhA) convened the Biologics and Biosimilars Stakeholder Conference on November 30, 2016, in Washington DC. The objectives of the Conference were to determine the key issues and challenges within the marketplace for biologics, follow-on biologics (FOBs), and biosimilars, identify potential roles and responsibilities of pharmacists regarding biologic and biosimilar medications, and identify actions or activities that pharmacists may take to optimize the safe and cost-effective use of biologics and biosimilars.

Data sources: National thought leaders and stakeholder representatives, including individuals from the Food and Drug Administration, Centers for Medicare and Medicaid Services, a private third-party payer, manufacturers, and several national organizations of health care professionals, participated in the conference. Information shared by this group was supplemented with relevant legal and regulatory information and published literature.

Summary: Biologics play a valuable role in the treatment of numerous health conditions, but their associated costs, which tend to be greater than those of small-molecule drugs, place a burden on the health care system. Biosimilars (both noninterchangeable and interchangeable) are highly similar copies of the originator biologic and offer the potential to reduce costs and improve patient access to biological products by increasing treatment options and creating a more competitive market. Despite the potential benefits of biosimilars, certain factors may limit their uptake. The conference participants explored issues that different stakeholders think influence the use of biologics, including biosimilars, in the United States. Barriers included technology, prescriber–pharmacist communication, legislation and regulations, limited patient and health care practitioner knowledge of biological products, patient and health care practitioner perceptions of biosimilars, and evolving science or lack of long-term data. After participants identified issues, they discussed strategies to address these concerns, including the need to enhance the education of pharmacists, prescribers, and patients regarding biologic products, including biosimilars and FOBs; the passage of state laws and regulations that do not impede the use of biosimilars, including interchangeable biosimilars; the use of product-specific tracking information in electronic health records and surveillance systems; bidirectional communication among pharmacists, prescribers, and other members of the care team to support pharmacovigilance and the maintenance of accurate patient records; and the development of evidence-based third-party payer policies.

Conclusion: Patient access to safe and cost-effective treatments is an important goal for the health care system. As the availability and use of biosimilars, including those determined to be interchangeable, increases, their potential to lower costs and improve patient access to treatment grows. However, the extent of such growth is, in part, dependent on various stakeholders' decisions to provide, pay for, or use these products in a safe and thoughtful

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* **Correspondence**: Jann B. Skelton, BSPharm, MBA, President, Silver Pennies Consulting, 17 Spruce Rd., North Caldwell, NJ 07006.
E-mail address: jskelton@silverpennies.com (J.B. Skelton).

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manner. Ongoing stakeholder collaboration, educational activities, and review of current government or payer policies are required to optimize the uptake of biological products, including biosimilars.

The American Pharmacists Association (APhA) convened the Biologics and Biosimilars Stakeholder Conference on November 30, 2016, in Washington, DC. The objectives of the conference were to determine the key issues and challenges within the marketplace for biologics and biosimilars, define the roles and responsibilities of pharmacists regarding biologic and biosimilar medications, and identify actions or activities for pharmacists to minimize barriers and challenges to optimize the safe and cost-effective use of biologics and biosimilars. In many cases, the principles discussed regarding biosimilars are applicable to follow-on biologics (FOBs), which are similar conceptually but have a different approval pathway. National thought leaders and stakeholder representatives including individuals from the Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), a private third-party payer, manufacturers, and several national organizations of health care professionals participated in the conference (see Acknowledgments). The conference featured presentations regarding various issues affecting biologics, including biosimilars, followed by robust discussion.

Originator biologics and biosimilars: Background and current issues

Biological products are substantially more complex than small-molecule drugs. According to the FDA's recent draft guidance, biological products can be complex chains or combinations of sugars, amino acids, or nucleic acids or living entities such as cells and cellular therapies.[1] Some of the first biologics marketed in the United States included human insulin, erythropoietin, growth hormones, and cytokines, whereas many of the recently approved biologics are monoclonal antibodies.[2,3] Monoclonal antibodies tend to have a larger molecular size, complex protein structure, and post-translation modifications.[4] Thus, when considering the complexity of biological products compared with small-molecule drugs, it is important to be aware that there are also variable degrees of complexity among biological products.

An important distinction between small-molecule drugs and biological products is the manufacturing process. Small-molecule drugs are generally produced through chemical synthesis, whereas biological products are manufactured through the use of living systems.[5] Biological products are sensitive; variable conditions can alter the biological product's structure, resulting in potential changes in their safety and efficacy. Therefore, they require consistent manufacturing and must adhere to specific storage and handling instructions.

Biologics have transformed the treatment of numerous health conditions, including anemia, cancer, autoimmune disorders, diabetes, and autoimmune/inflammatory diseases. Although they have the potential to confer great patient benefit, they are generally associated with high costs. They represent a growing share of overall global pharmaceutical sales. In 2002, $46 billion was spent on biologics globally and accounted for 11% of overall pharmaceutical sales. In 2017, these products are expected to account for $221 billion in sales annually and represent 19%-20% of total global pharmaceutical spending.[3] It is expected that by 2020, the global market for biologics will exceed $390 billion and account for up to 28% of total pharmaceutical spending.[6] Trends in the United States mirror these global trends, with more than $41.7 billion spent on biologics in 2013, with costs increasing as more products enter the market.[7]

The patents for several biologic products are approaching expiration. It is estimated that biological products representing $29 billion of sales in the United States will lose their patent protection by 2020.[8] Biosimilars offer the opportunity to provide significant cost savings by increasing competition, although estimates on the extent of potential savings vary greatly.[7] The extent of these savings will be influenced by the difference in price between the originator biologic and competing biosimilar products, as well as utilization or market penetration of the biosimilar products. Product acceptance by patients and health care providers, the extent to which there is clinical variability between innovator and biosimilar and interchangeable biosimilar products, as well as formulary design and utilization management programs developed by third-party payers can all affect products' utilization or market prevalence.[9]

As noted above, biologics are complex molecules that are often sensitive to changes in the manufacturing process and require special storage and handling. Developing an exact copy of a biologic agent is, at present, technologically impossible, and in fact, even serial batches of the reference product have some degree of variability.[10,11] As a result of this variability and other factors, the generic drug approval processes used for small-molecule drugs are not appropriate for biosimilars. The biosimilar approval process requires the biosimilar to be shown to have the same effectiveness and safety as the reference brand.

Overview of federal legislation and agency activity

Biological products and small-molecule drugs are approved through different pathways. In general, the Food, Drug, and Cosmetic Act (FDCA) allows for approval of small-molecule drugs following a new drug application (NDA), and the Public Health Services Act (PHSA) allows for approval of biologics following a biologics license application; however, some biologics, including FOBs, are approved under the FDCA.

Generic drug approvals for small-molecule drugs are authorized by the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act), which amended FDCA to create the 505(j) and 505(b)(2) abbreviated pathways. The 505(j) pathway is used for approval of generic drugs that are similar to the innovator

product's active ingredient(s), strength, dosage form, route of administration, quality, and performance characteristics. Alternatively, the 505(b)(2) pathway may be used for a drug that, despite having significant differences, is sufficiently similar to an approved drug. Both pathways require an NDA. FDA approved a limited number of biological products, such as insulin, calcitonin, and human growth hormone, which are referred to as FOBs, under FDCA. Although similar biological products developed in the late 1970s and early 1980s have been regulated for decades under FDCA, this approach is considered to be inadequate for the current biological products environment.

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) created an abbreviated approval pathway (the 351(k) pathway) for biological products "highly similar" (biosimilar) to or "interchangeable" with FDA-approved biologics (referred to as reference products).

To facilitate BPCIA implementation, FDA has developed guidance documents regarding biological products, including biosimilars, to help inform stakeholders of the agency's thinking on biological products licensed under PHSA.[12] In January 2017, after the conference, FDA finalized 2 guidance documents, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" and "Nonproprietary Naming of Biological Products," and released a long-awaited draft guidance regarding biosimilar interchangeability, "Considerations in Demonstrating Interchangeability with a Reference Product." This draft guidance clarifies how FDA will review applications seeking to demonstrate interchangeability. As of the time of this writing, FDA has approved 4 biosimilars but has not made any determinations regarding interchangeability; however, the release of the draft guidance may spur applications seeking this determination. It is important to note that the Affordable Care Act (ACA) required all biologics to be approved and regulated under PHSA. This includes biologics previously approved under FDCA, which are subject to a transition period until March 23, 2020.

Biosimilarity

Because the reference product previously conducted clinical safety and efficacy studies to support initial product approval, the biosimilar approval process allows a biosimilar manufacturer to rely on comparative data with the reference product and therefore relies to a greater extent on analytic studies that demonstrate similarity than on clinical trials that demonstrate efficacy and safety.[13] Information for demonstrating biosimilarity is based on a totality-of-evidence approach that evaluates analytic studies, nonhuman animal studies, and clinical data including the assessment of immunogenicity, pharmacokinetics, and pharmacodynamics.

More extensive or additional clinical trials may be required by FDA if there are residual uncertainties about the product's similarity to the reference product. In addition to demonstrating that the biosimilar product is highly similar to the reference product, the manufacturer must demonstrate that the biosimilar has the same mechanisms of action (to the extent that it is known), route of administration, dosage form, and strength and meets appropriate manufacturing standards. As a scientific matter, the biosimilar application is expected to include at least 1 clinical study that includes a comparison of the immunogenicity of the biosimilar and associated reference products.[13]

Interchangeability

As stated above, BPCIA also created a category for biosimilar products that are determined to be "interchangeable." In addition to being considered biosimilar, interchangeable products are expected to produce the same clinical result as the reference product in any given patient. If the product is administered more than once to a patient, there must not be any increased risk to safety (e.g., immunogenicity) or diminished efficacy when alternating or switching products, compared with using only the reference product. The FDA's draft guidance on interchangeability provides an overview of important scientific considerations in demonstrating interchangeability with a reference product, including consideration for the design and analysis of a switching study or studies to support a demonstration of interchangeability and consideration for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products.[14]

According to BPCIA, pharmacists may substitute interchangeable products for the reference product without the authorization of the prescriber and pending state law requirements. Thus, an interchangeability determination could make a product more competitive with the reference product as there is greater access to the interchangeable product at the pharmacy level. It is also important to note that BPCIA grants the first interchangeable biological product to a given reference product a 1-year exclusivity period during which no other interchangeable biologic to that reference product may be marketed.[15]

Conditions of use

Biosimilar manufacturers may extrapolate clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.[16] However, FDA permits extrapolation only if sufficient scientific justification is provided. This justification may be based on information such as the target/receptor(s) for each relevant activity/function of the product, the immunogenicity of the product in different populations, and differences in expected toxicities in each condition of use and patient population. Furthermore, a biosimilar cannot be approved for indications for which the reference product has orphan or pediatric exclusivity. Thus, a biosimilar may not have all of the indications that its reference product bears. As a result of this approval framework, it is possible for there to be multiple biosimilars for the same reference product with differing arrays of approved indications.[17]

Draft guidance from FDA regarding the labeling for biosimilars lists several requirements. The labeling should state that the product is a biosimilar and should also have the same or fewer conditions of use (e.g., indication(s), dosing regimen(s)) compared with the reference product.[16] If the biosimilar applicant obtains licensure for fewer than all of the reference product's conditions of use, then the labeling between the reference product and biosimilar will vary. However, to help ensure safe use, there may be circumstances where a biosimilar's label must include information relating to an indication or indications for which the biosimilar application did not seek licensure.

State-level policy issues with biologics and biosimilars

Although the FDA makes the determination regarding whether a biosimilar product is interchangeable with the reference product, drug substitution is under the legal authority of states. Therefore, individual states may pass laws that may affect the utilization of biosimilar and interchangeable products. FDA helps facilitate substitution by maintaining resources such as the Orange Book (which lists small-molecule drugs and therapeutically equivalent generic drug products) and the Purple Book (which lists biologic and biosimilar or interchangeability evaluations) that can help inform health care practitioners making substitution decisions.[18,19]

State laws and regulations regarding product substitution have the ability to facilitate or hinder the use or uptake of biosimilar and interchangeable products. Overly restrictive state laws not only erect logistical barriers to the use of biosimilars, but also can undermine patient and prescriber confidence in these products. Laws that facilitate biosimilar use can stimulate a more competitive marketplace.

As of 2016, 25 states and Puerto Rico have passed laws relating to substitution for interchangeable biosimilars. These laws address various aspects of requirements that affect whether a biosimilar may be substituted for a biologic reference product and the steps that must be taken to do so, including record keeping, notification requirements, and requirements to notify and obtain approval from the patient. Although there is significant variability among states, there is also much commonality (Table 1).[20] The Academy of Managed Care Pharmacy maintains a webpage with information about state laws, legislation, and regulations regarding biosimilars at: https://www.biosimilarsresourcecenter.org/map/.

Product naming and impact on practice and pharmacovigilance

The conventions for determining nonproprietary names for biosimilars have important implications for pharmacy systems, institutional formulary management, including electronic ordering and dispensing, and pharmacovigilance activities. If all biosimilars associated with the same reference biologic have identical nonproprietary names, the FDA thinks that it would be more difficult to easily track specific biosimilar products and their effects. On the other hand, the use of related but unique names may facilitate pharmacovigilance, but it is different than for small-molecule drugs and may cause confusion in practice with product substitution and interchangeability. The concerns raised by both sides of the naming issue had been continually voiced to the FDA as the agency determined a naming structure for biological products.

In January 2017, the FDA finalized naming guidance: "Nonproprietary Naming of Biological Products"; however, the information collection provisions in this guidance regarding submission of proposed suffixes are under Office of Management and Budget review and are not for current implementation. The guidance clarified that, generally, biological products will include a "core name" and a 4-letter suffix that is devoid of meaning.[21] The core name is to be consistent with the name designated by the United States Adopted Names Council (USAN) (described in more detail below). For example, 2 biosimilars for the fictional reference product replicamab from different sponsors might be called "replicamab-cznm," and "replicamab-hixf."[21] In addition, the guidance notes that applicants may submit a list of 10 preferred suffixes from which the FDA may select 1 or none. The naming process described in the guidance is significantly different from that of small-molecule drugs, for which USAN essentially determines the nonproprietary name.

In the United States, nonproprietary names for active ingredients of medications, including biologics, are approved through USAN. USAN is sponsored by the American Medical Association, the United States Pharmacopeial Convention (USP), and the APhA. As medicines are approved or licensed, the USP develops a drug substance monograph and creates an official title that aligns with the USAN nonproprietrary name.[22] USP also establishes a nonproprietary name for drug products. When the FDA approves a drug or licenses a biologic and there is already an applicable USP standard, the official title in the USP monograph is the designated nonproprietary name. If there is no applicable USP standard, the FDA assigns an interim name that serves as the nonproprietary name until the USP creates an applicable monograph.

Of note, to date USAN and the USP do not assign a 4-letter suffix to the nonproprietary name of medications or their active ingredients. It is also important to note that the World Health Organization has a naming process to assign an international nonproprietary name that is different from that of the USAN, USP, and FDA. Thus, biological product naming is inconsistent between key stakeholders and varies from naming processes for small-molecule drugs. FDA's recent

Table 1
Common features of state laws regarding biosimilar substitution

Feature	Details
FDA approval	Any biological product under consideration for substitution must first be approved as "interchangeable" by FDA.
Prescriber decides	The prescriber is able to prevent substitution by indicating "dispense as written" or "brand medically necessary" on the prescription.
"Notification" vs. "communication"	Some laws require that the prescriber "must be notified" of any substitution made at a pharmacy. Others state that the pharmacy must "communicate with" the prescriber, allowing a notation in an electronic health record.
Patient notified?	The patient must be notified that a substitution has been made; in some cases, the patient must provide consent for the substitution.
Records	Pharmacists and prescribers must retain records of substituted biological products.
Immunity	Some state laws provide pharmacists with immunity for making substitutions in compliance with state law.
Public information	The state must maintain a public or Web-based list of allowed interchangeable products.
Cost or pricing	Some laws require pharmacists to explain the cost or price of the biologic and the interchangeable biosimilar. Others require that a substituted product must have the lowest cost of the available options.

Source: National Conference of State Legislatures.[20]

naming guidance clarifies that the agency will utilize a different naming process, however the USAN nonproprietary name for active ingredients will still be used but FDA has deemed it to be the "core name."[21]

The National Council for Prescription Drug Programs (NCPDP), which develops consensus-based standards and industry guidance for the health care industry, has developed recommendations to standardize best naming practices for all new drug entities and biologics, including biosimilars. NCPDP has recommended against different naming practices for biologics. According to NCPDP,[23] applying different names for the same biological drug ingredients

- Introduces confusion and unnecessary complexity.
- Conflicts with normal pharmacy practice.
- Is unnecessary for product recall or other patient safety considerations.
- Undervalues the ability of existing systems (e.g., National Drug Code (NDC)– and lot-based recalls) and new regulatory structures (track and trace) to provide adequate safeguards.
- Affects clinical decision making, including the ability to identify therapeutic alternatives.
- May affect safety for patients.

Implementation issues and ongoing stakeholder concerns may come to light following FDA's finalized naming guidance, because there continue to be opposing views from key stakeholders on the need for distinct naming for these products. The effectiveness of pharmacovigilance efforts, including those that rely on the 4-letter suffix and alternate methods (e.g., tracking using the NDC), remain to be seen, compared, or combined. In addition, currently, pharmacy and other health care technology systems may not have the capability to handle suffixes.

Current market uptake of biosimilars

The first biosimilar in the United States was approved in 2015, followed by 3 more in 2016 (Table 2). However, as noted above, several biological products have been approved as FOBs, which is similar conceptually to a biosimilar but uses a different regulatory pathway. Many more biosimilars are in the pipeline. In 2016, the FDA reported that there were 66 biosimilars to 20 different reference products enrolled in their biosimilar development program.[24] Even more are in earlier stages; the Biotechnology Information Institute identified 797 biosimilars in development as of January 2017.[25]

Prescriber knowledge and attitudes regarding biosimilars will be critical determinants of uptake as more products enter the market. Information on actual prescriber decision making regarding biosimilars in the United States is not well established owing to limited market experience. One survey of 1201 U.S. physicians conducted from November 2015 to January 2016 regarding knowledge and attitudes about biosimilars found several educational needs and areas of concern.[26] For example, only 45% thought that biosimilars would be safe and appropriate for use in both treatment-naive and existing patients. In addition, 36% thought that a biosimilar would be less safe than the reference biologic. Across physician specialties, survey respondents considered that their specialty associations would be the primary trusted sources of information.[26] Respondents were interested in learning more about several topics related to biosimilars: 76% were interested in more information about the safety, efficacy, and potency of biosimilars; 65% wanted to learn more about interchangeability; and 62% wanted to learn more about the costs of biosimilars.[26]

A survey of 781 pharmacists regarding naming conventions for biosimilars found that the use of a nonproprietary core name with a suffix was preferred by 48% of respondents. The use of a nonproprietary core name alone was preferred by 26%, and smaller percentages preferred the use of a nonproprietary core name with a prefix (14%) or the use of a unique brand name (11%).[27] In contrast, participants reported higher levels of confidence when the biosimilar and reference biologic shared the same nonproprietary name. In addition, the majority indicated that providing notification to prescribers after the dispensing of biosimilars would be an added burden.[27,28]

Table 2
Biosimilar products approved in the United States as of November 2016

Brand (proprietary) name	Proper (nonproprietary) generic name	Approval date
Zarxio	Filgrastim-sndz	March 2015
Inflectra	Infliximab-dyyb	April 2016
Erelzi	Etanercept-szzs	August 2016
Amjevita	Adalimumab-atto	September 2016

Pharmacists' roles regarding biological products

Biological products, including biosimilars, are dispensed and administered in a variety of health care facilities and settings. Pharmacists have many roles related to the choice and utilization of biological products, which may vary across practice settings, such as community pharmacies, health-system pharmacies, specialty pharmacies, and offices or clinics of physicians and other health care providers. In addition, although pharmacists have certain roles currently related to biological products, the roles and responsibilities of pharmacists have been evolving to adapt to new care models and demands from patients, other providers, and the health care system generally.[29]

As medication experts, pharmacists provide education about all medications, including biological products, to patients, their caregivers, and other members of the health care team. They may be involved in assessing whether a particular therapy is appropriate for a patient, as well as in evaluating the role of a biologic in a patient's overall treatment regimen. Pharmacists often play key roles in assessing a patient's response to therapy, including adverse event monitoring and supporting patient adherence. If a biosimilar is available, pharmacists may recommend the biosimilar product to prescribers or substitute interchangeable products in accordance with state laws and regulations.[30-32] They may also educate other members of the health care team regarding the biosimilar approval pathway, including the scientific rigor of the process.

Pharmacists may be involved in pharmacy and therapeutics (P&T) committees and have key roles in evaluating the placement of biological products on formularies and making recommendations regarding the use of various drug use

management strategies.[29,33] From a patient care perspective, pharmacists may explain formulary requirements to patients and prescribers, and may perform administrative duties (such as complying with prior authorization requirements) to ensure that the patient receives the most appropriate therapy. Pharmacists may provide patient care services, such as medication therapy management, to patients to help optimize outcomes in patients who use biological products, including biosimilars.[34]

Stakeholder perspectives on issues related to biologics and biosimilar uptake

Participants in the conference engaged in a robust discussion on key issues affecting the biological product marketplace. The content of that discussion is described below.

State activity

Participants noted that it would be crucial for a variety of stakeholders to advocate at the state level for policies that support patient access to biosimilars to support market uptake. They thought that current state laws are not clear and that some recently passed laws and regulations may inappropriately impede the use of biosimilars. Participants discussed the need for lawmakers and other policymakers, in addition to providers, pharmacists, and patients, to be educated on biologics, including biosimilars and FOBs. For example, they noted that biological products with product exclusivity and biosimilarity or interchangeability evaluations are listed in the FDA's Purple Book. Nevertheless, some state laws regarding biosimilars indicate that a biosimilar must be listed as therapeutically equivalent to the reference product in the FDA's Orange Book, which lists approved drug products and therapeutically equivalent generic products that are bioequivalent. Whereas an FOB may be listed in the Orange Book, biologics and associated biosimilars are not, and they are not tested for therapeutic equivalence, so these laws have set an unreasonable and inappropriate standard for substitution and subsequently may need to modified to be in alignment with the FDA's Purple Book.

Electronic health records, pharmacovigilance, and access to data

Stakeholder participants explored a number of issues regarding how biologics and biosimilars are to be recorded and monitored through electronic health records (EHRs) and pharmacovigilance systems. The FDA has cited the need for better tracking of products for pharmacovigilance as a reason for the need for unique names for biological products. Participants noted that there are already several existing systems that allow for post-marketing surveillance and pharmacovigilance of biologics and biosimilars, including voluntary adverse event reporting, the FDA's Sentinel system, the Academy of Managed Care Pharmacy's (AMCP) eDossier system, and other established programs. The Sentinel system is a national electronic system for monitoring the safety of FDA-regulated medical products, including biologics and biosimilars. AMCP's eDossier system is a Web-based tool that provides qualified health care decision makers the opportunity to easily review, evaluate, and compare products to make informed evidence-based decisions and offers another resource for ongoing product evaluations.

Post-marketing surveillance and pharmacovigilance systems rely on accurate tracking and recording of the specific product that a patient received. As opposed to a suffix, some stakeholders favored a tracking system that uses a brand name, and others advocated a tracking system that uses NDC. The NDC serves as a universal product identifier for human drugs that identifies the labeler (e.g., manufacturer, repackager, or distributor), product, and trade package size. NDCs are usually found on the drug label or outer packaging and may be used in billing and on medical claims. Some participants favored the use of NDCs for tracking rather than a suffix, in part because the NDC is already used for all drugs, not just biologics, and because they thought that current issues in tracking would not be corrected by the use of a suffix.

Participants reported that, although pharmacy systems allow for tracking with the use of the NDC, most pharmacy systems do not have the functionality that allows tracking and reporting back to the prescriber the specific product dispensed. Likewise, pharmacists may not be able to access information that would be helpful in recommending a particular biological product. In addition, pharmacists often do not have access to a patient's EHR, and even less frequently do they have the ability to add to or modify EHRs. Participants indicated that stakeholder collaboration is needed to facilitate bidirectional flow of information between members of the care team that would be good for overall patient care.

During the discussion, participants noted that NDCs are not used in all settings (e.g., in-patient hospitals) where biological products are dispensed and/or administered. In other health care settings, such as physician's offices, J codes are most commonly used when billing medications, because they are part of the Healthcare Common Procedure Coding System (HCPCS), which is based on Current Procedural Terminology (CPT). CPT codes are used to bill outpatient and office procedures, and there are few CPT codes that can be billed by pharmacists. Participants noted that unlike NDCs, J codes are not always product specific and therefore may not provide the necessary information for pharmacovigilance, tracking, and documentation. However, though it was not discussed during the meeting, it is important to note that as of 2016, CMS groups all products that are biosimilar to the same reference product into a single HCPCS code and assigns manufacturer-specific modifiers to specific biosimilars in each HCPCS code. Reference products maintain their own unique HCPCS codes. CMS also permits use of a miscellaneous HCPCS code for new biosimilar products that are not adequately described by an existing HCPCS code.

Participants recommended ensuring that all entities that dispense and administer biological products create and maintain patient records containing information on the specific products received by the patient. Stakeholder participants felt that it is essential to address the lack of consistent and accurate NDC use in some settings and suggested documenting the dispensed/administered product's NDC in all practice settings. Participants stressed that it is important to develop systems that ensure that the correct NDC number is recorded when these codes are used. (Participants suggested that office staff may inadvertently code biosimilar products as the

reference product out of habit.) This is an issue for pharmacovigilance and ensuring that any adverse events are attributed to the correct product, as well as for billing of manufacturers for rebates (e.g., in Medicaid). Participants noted that, owing to issues with the accuracy of physician-administered drug reports, the Office of the Inspector General is currently examining state compliance with requirements for rebates for drugs administered outside pharmacies. Furthermore, although there are stringent record-keeping requirements for pharmacies, not all state laws have the same requirements for physicians and other members of the care team.

Participants noted that serialization and barcoding of products, which are expected to be implemented in the future pursuant to federal law, and may be effective strategies to address some of these concerns.[35] However, the FDA and others think that suffixes or other naming mechanisms to distinguish between products are needed to better track these products and prevent inadvertent substitution.[21]

Payer decision making

Stakeholders felt strongly that payers should evaluate a variety of factors when determining access to biologics and biosimilars within formularies and recommended that payers evaluate clinical, humanistic, and economic outcomes when implementing use management strategies (e.g., formulary tiers, step therapy, prior authorization).

Participants noted that because many biologics are infused or injected in a physician's office, outpatient clinic, or home infusion center, these products are often managed as part of the medical benefit rather than the pharmacy benefit. Medical benefits, including HCPCS codes, which may not provide sufficient detail, often do not support the level and complexity of use management strategies that are regularly used to manage the pharmacy benefit. As a result, participants noted that use strategies to manage biosimilars may represent the first time that such strategies are used within the medical benefit.

Stakeholders representing payer organizations noted that several payers are exploring strategies to encourage biosimilar use. For example, Medicaid programs generally consider biological and biosimilar products to be covered outpatient drugs and therefore view the introduction of biosimilars as an opportunity to achieve cost savings and improve beneficiary access to treatment. (Medicaid managed care organizations must provide coverage of outpatient drugs that is consistent with what is provided under Medicaid fee-for-service programs.) Stakeholders noted that CMS also encourages Medicaid programs to use drug utilization and cost management tools (i.e., step therapy, prior authorization processes, and preferred drug lists) for biologics and biosimilars to achieve cost-effective clinical outcomes.

One stakeholder noted that CMS's payment system for biologics and biosimilars establishes a level playing field. Biosimilars would be reimbursed based on their average sales price (ASP) plus a percentage of the ASP of the reference product. As a result, the margin would be the same regardless of whether the reference product or a biosimilar is used.

The private insurance market also is exploring options to integrate and support the use of biosimilars. Private third-party payers often provide coverage for biologic therapies through a specialty formulary tier and may apply use management strategies to these products. Conference participants engaged in vibrant discussion regarding strategies being used by third-party payers as biosimilars are implemented in the marketplace. They noted that payers are being challenged by the growing number of biologics and their associated costs, which are projected to continue rising owing to the number of products in the pipeline. Payers view biosimilars as a strategy to ameliorate these costs. They noted that policies established by third-party payers, including formulary decisions and use management strategies, would strongly influence the uptake of biosimilars and the resulting impact on costs of care.

Stakeholders noted that only filgrastim-sndz (Zarxio) has been on the market in the United States long enough to gather preliminary data regarding market uptake and the extent of pricing discounts. According to data shared by stakeholders during the conference, organizations saw an increase in provider willingness to prescribe the biosimilar filgrastim-sndz throughout 2016. One stakeholder reported that by the end of 2016, approximately 30% of prescriptions within their organization were for the biosimilar product, and the biosimilar product would be given preferred status in their formulary in 2017. Another stakeholder noted that, as of November 2016, data regarding this product indicated that it offers a list price difference of about 15%, and although oncologists initially expressed reluctance to use the biosimilar, the market share of the innovator product has been reduced by about one-third.

Stakeholders did note that because filgrastim is not used chronically, filgrastim-sndz may have had greater acceptance from health care professionals and patients than other biosimilar products that are approved for treatment of chronic conditions and may require patients to switch products. Some stakeholders thought that switching medication of patients suffering from chronic condition(s) may be more challenging, particularly for some therapeutic categories, such as rheumatology, when the patient is stable on their current treatment regimen.

Participants noted that in 2016, the British Society of Gastroenterology (BSG) issued a guidance regarding the use of infliximab and associated biosimilars (biosimilars of infliximab were approved in Europe in 2014). The BSG statement indicated that either the reference product or one of the available biosimilars may be used for patients who are initiating therapy, and cost should be taken into account during product selection. It also indicated that there is sufficient evidence to recommend that patients who are stable or in remission on the reference product may be switched to the biosimilar to reduce costs, but this should be done in consultation with the patient. The guidance also noted that automatic substitution at the pharmacy without consultation with the prescriber is not appropriate.[36]

Identifying opportunities and mechanisms to foster and streamline biosimilar use

The European experience

Several participants expressed interest in the use of biosimilars in Europe to inform decision making in the United States, particularly when considering patient care issues. A European pathway for biosimilars was created in 2004, and

the first biosimilar reached the European market in 2006. Since that time, there have been more than 400 million patient-days of exposure to biosimilars in Europe, providing an abundance of information that can be evaluated when considering biosimilar adoption in the United States.[37]

Although it is not identical to the U.S. market, there are opportunities to learn from the European experience to inform processes in the United States. For example, participants cautioned that some terms are defined differently in Europe, and decisions about switching and substitutions are deferred to the individual European countries. Therefore, when analyzing the European experience, stakeholders must clarify which activities are defined by which terms.

Participants all agreed that there were no safety issues detected in Europe related to biosimilars that were not also observed with use of the reference products, and they noted that there is growing support from some specialty societies for the use of biosimilars in the United States. However, there are other specialty groups who are concerned about switching between biologics, including biosimilars, and oppose mechanisms to make biological product substitution easier.[36]

Patient care

Conference participants discussed several patient care issues that affect pharmacists who care for patients receiving biosimilars. For example, they noted that product-specific tracking in EHRs would be important for patient care for a variety of reasons beyond pharmacovigilance. They noted that the goal of maintaining an accurate and current medication record that can be shared among providers is a general issue that has been championed by pharmacists as a strategy to improve patient safety and quality of care. Participants noted that even with the use of EHR systems, and with strong stakeholder support, this goal has not been achieved.

The possibility that the specific product administered to a patient could be recorded inaccurately or could be impossible to identify owing to the use of J codes or a naming system that includes suffixes could further impede the goal of accurate patient medication lists and complicate medication reconciliation and appropriate management of transitions of care. Furthermore, participants noted that bidirectional EHR functionality is essential to efficiently and effectively communicate any changes at the community pharmacy or point of administration to the health care team. It is important to ensure that product switches and substitutions are accurately recorded in a patient record, so necessary health care personnel have appropriate access.

Regarding biosimilar naming, participants noted that the use of suffixes devoid of meaning to identify specific biologic products may pose challenges for patients and health care providers considering use of a biosimilar. Some participants noted that providers will need to be familiar with and prescribe biosimilar brand names because patients are unlikely to remember meaningless suffixes. In addition, patients may become less involved in, and aware of, their care decisions if they have difficulty identifying medications.

Another patient care issue that was identified for pharmacists is the stocking of biosimilar products and whether practice sites will need to stock all biosimilars that are available for a specific reference product. Participants discussed the fact that although biosimilars may be associated with lower costs than an originator biologic, they can still be very expensive, and inventory cost management is a real concern. Although some participants thought that community pharmacies would be unlikely to carry all available biosimilars, others thought that it was possible that different payers may have formulary preferences for different biosimilars as a result of contracting and rebates, and that stocking decisions would be driven by payer formularies and use management strategies. In addition to affecting pharmacists' buying decisions, third-party coverage or payer formularies may also affect patients' treatment options. Pharmacists will need to be prepared to navigate such structures once implemented.

Participants also recommended that pharmacy benefit managers and other third-party payers proactively notify pharmacies and prescribers when there is a formulary change. Stakeholders reported that patients and the health care team are often unaware of formulary changes until the patient reaches the point of sale in the pharmacy, creating logistical challenges and possibly delaying access to treatment. Increased communication could both streamline patient care processes and allow pharmacists to more effectively manage inventory.

Switching, interchangeability, and substitution

Participants noted that pharmacists will have key roles in determining whether a patient receives an interchangeable biosimilar product, and therefore will have an important effect on biosimilar market uptake. As discussed earlier, drug substitution laws are developed and implemented at the state level and vary in their requirements. Therefore, pharmacists will need to access resources such as the Purple Book to identify which products are interchangeable, paying careful attention for situations in which biosimilars are not interchangeable for all conditions of use. They also will require education about interchangeability, substitution, individual state requirements, and relevant products to be prepared to dispense these products appropriately, provide notifications in an efficient and nonintrusive manner, and answer any questions that arise from the patient or prescriber.

Education and training

Stakeholders identified a variety of educational needs related to biological products, including biosimilars, to improve understanding and the impact of coverage and other policies that may affect product selection. Although participants acknowledged the need for biosimilar-specific education, there was general agreement that education regarding all biological products is also needed. Stakeholders were concerned that education specific to biosimilars may not adequately communicate issues that pertain to all biological products. For example, health care practitioners may misperceive the safety of biosimilars if best practices regarding storage and transportation are only communicated in education pertaining to biosimilars and the health care practitioner does not receive education regarding biological product storage and transportation.

Pharmacists have a central role in providing education and communicating with patients and other members of the health care team about medications. Therefore, it is crucial for

pharmacists to be knowledgeable about biosimilars to support acceptance and appropriate utilization of these products. As the medication experts on the health care team, pharmacists have educational roles beyond patient education and counseling during dispensing, including within specialty pharmacy as well as with health plans and P&T committees that support appropriate formulary changes. Pharmacists who practice in specialty pharmacy and work under collaborative practice agreements may have additional roles in the selection of biosimilar products.

It is expected that use management techniques will continue to be used for biological products to affect product selection and steer patients and providers to effective and safe lower-cost options. Pharmacists and physicians will need to be knowledgeable about biological products, specifically and as a class, as well as real or perceived concerns, to discuss available treatment options with patients. Of note, switching among some products may require a change in the type of administration device used for a product, and pharmacists will need to be prepared to educate patients about appropriate administration techniques.

Conference participants identified several topics that will be important to communicate in educational initiatives for pharmacists. These include

1. Terminology associated with biological products, including the definition of a biosimilar, an FOB, an interchangeable product, bioequivalence, why biosimilars are not considered bioequivalent, and distinctions between substitution and switching.
2. The approval pathways for biological products, including the sophistication and rigor of the analytic approach used to approve biosimilar products, additional requirements for interchangeable products, and the possibility of extrapolation.
3. Laws and regulations addressing biological products, including naming conventions and state-level requirements for biosimilar product switches.
4. Strategies used for ongoing safety monitoring, including lessons learned from European experience.
5. Dispelling misperceptions, such as that biosimilars are generics, that they are considered to be "therapeutically equivalent," that they are listed in the Orange Book, or that interchangeable products are held to a higher, rather than different, approval standard than other biosimilars (implying that biosimilars are held to a lower standard).
6. Labeling requirements, including how requirements for biosimilars differ from those for biologics and what real or perceived information is gleaned from biosimilars having different approved conditions (among biosimilars of the same originator product as well as between biosimilar and originator).
7. Available resources that address biologics and biosimilars (e.g., FDA's Purple Book and online educational tools).

Strategies for delivering education

Conference participants also discussed strategies for delivering education programs to pharmacists, prescribers, and patients. They stressed the need for ongoing and consistent messaging among all health care professionals as well as patients. For example, biosimilars are sometimes erroneously referred to as generic versions of biologics, which may be confusing for patients if they hear conflicting information from different members of their health care team. The term "generic" has a strict regulatory definition as well as a common lay definition. Clarifying this distinction would help patients to understand biosimilars.

Participants highlighted several educational initiatives regarding biosimilars that are already underway. For example, the FDA has an active education outreach program that provides education to health care providers to improve knowledge and understanding of biosimilars and interchangeable products.[38] The FDA is also engaging in listening meetings to gather input from prescribers and patients to determine additional needs for education and outreach.

Based on research that revealed that physicians consider their most trusted and reliable sources of information to be peer-reviewed publications and specialty societies of their peers,[25] the group felt strongly that professional associations should focus on developing educational activities about biological products and form collaborations with other organizations to develop interprofessional resources. Educational strategies that are pharmacist specific would likely need to be further tailored based on setting, such as a specialty pharmacy, hospital, or community-based pharmacy.

Stakeholders offered support for the development of a continuing education road show, train-the-trainer program, and certificate training program to provide more comprehensive education and training about biological products. They recommended collaboration with the American Association of Colleges of Pharmacy to support the integration of biological product information in the curricula of schools and colleges of pharmacy.

In addition to continuing education activities, participants thought it would be important for professional organizations to make biosimilar education a priority and disseminate information through multiple channels, such as regular articles in professional publications.

Suggestions to provide education to those constituencies were provided, such as partnership with patient and consumer advocacy organizations. Participants reported that patients are likely to look to their patient advocacy organizations as the trusted source of information and are generally more receptive to information from their peers who understand their disease condition and associated struggles and fears. Therefore, forming partnerships with patient advocacy organizations for messaging and including information in patient advocacy newsletters and similar communication channels would likely be an effective patient education strategy. Participants also recommended developing patient-friendly language to explain biosimilar concepts, using consistent terminology, and coordinating with third-party payers to support the use of this consistent terminology.

Evolving implications

Since the conference, significant changes at the national level occurred that may affect biosimilar use. As described previously, FDA released final guidances, "Nonproprietary Naming of Biological Products" and "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a

Reference Product," and a draft guidance, "Consideration in Demonstrating Interchangeability with a Reference Product." Although these documents establish policies related to biological product naming and set the stage for interchangeable approvals, the change in Presidential administration and discussions surrounding President Trump's efforts to repeal ACA, which includes the BPCIA, may have implications for stakeholders relying on the law and open up FDA's recent policies for further evaluation.

President Trump's Executive Order to "minimize the economic burden of the Patient Protection and Affordable Care Act pending repeal" may further affect BPCIA implementation efforts.[39] In addition, the Presidential "Memorandum for the Health of Executive Departments and Agencies" describes a regulatory freeze, where regulations and guidances that are pending review or published but have not taken effect will be delayed for at least 60 days from their effective date. Finally, another recently issued Executive Order, which may affect future FDA regulatory activity, requires all federal agencies to eliminate 2 regulations for every 1 issued. As demonstrated by the robust discussion during the Conference, significant efforts and resources have been devoted to foster use of biosimilars, and the biological product landscape will be greatly affected once FDA approves biosimilars that are interchangeable. Thus, BPCIA implementation delays may allow for additional policy changes and have implications for patient access to cost-effective medications, among other consequences.

Although biological products were not focused on during the election, drug pricing was a hotly debated issue. Given the potential for biosimilars to reduce pricing and the opportunity for both legislative and regulatory changes, along with anticipated changes in FDA leadership, certain policies addressing biological products may be called into question in the coming years. However, it remains clear that biosimilars will have a place in the U.S. health care system. Therefore, identifying and being aware of different stakeholders' concerns and needs may provide helpful insight to decisions related to biological products, and biosimilars in particular.

During the conference, participants identified top-line needs involving pharmacists in optimizing the impact and value of biologics (Table 3). Addressing each of these needs will require collaboration and is crucial to helping to prepare pharmacists, including student pharmacists, to manage the needs of patients receiving biological products, including biosimilars. However, attention should also be paid to study mechanisms that most effectively and efficiently satisfy these needs, and information should be shared freely to establish best practices and guiding principles from which others may learn.

Because health care providers often trust information from professional associations, and because patients are most likely to trust information from peer organizations, partnerships with these groups will be particularly important to the success of educational initiatives. However, it is important to note that not all stakeholder groups that will be affected by biologics and biosimilars were represented at the conference. For example, there was no representation from patient advocacy organizations, wholesalers that distribute biological products, or data compendia which deliver product information that permeates all facets of the health care system. Outreach and collaboration with such groups will be important to identify and address other key issues and concerns, such as educational needs and patient perceptions of biological products, including biosimilars.

Table 3
Pharmacists' needs for optimizing the impact and value of biologics

Bidirectional communication between pharmacists and prescribers within EHR systems.
Ability to identify the specific product that is dispensed across all practice settings, such as through the use of National Drug Codes in settings beyond community pharmacies.
Consistent messaging and terminology to discuss biological products, including biosimilar medications.
Clear communication of the roles and responsibilities of pharmacists in the care of patients being treated with biological medications, including biosimilars.
Evaluation and examination of European experiences with biologic and biosimilar products to gain insights into "lessons learned."
Educational programs that build foundational understanding and confidence around biologic products, including biosimilars. (This was noted as an important activity for state and national pharmacy associations and employers of pharmacists.)
Engagement of patient advocacy organizations to reach consumers with educational messaging related to biologic and biosimilar medications and the role of the pharmacist.
Integration of information about biologic and biosimilar medications in pharmacy school curriculums to facilitate better understanding of these products by all stakeholders.

In addition, because some agency activity regarding biosimilars has not yet been finalized or released, new issues affecting biosimilar uptake and integration in the market may arise.

Finally, although there is extensive experience in Europe that supports the adoption of biosimilars, pharmacovigilance efforts in the United States will be crucial to determining whether there are previously unidentified safety issues. It was noted that there is no need for special pharmacovigilance programs that single out biosimilars, but that the pharmacovigilance of biosimilars must be pursued with the same vigor as was applied to the reference product.

Moving forward, ongoing collaboration among all stakeholders, including policymakers at the state and federal levels, health care providers and associations, third-party payers, and patient advocacy organizations, will be needed to optimize the use of both biologics and biosimilars to provide value to the health care system and excellence in patient care. These efforts should include monitoring changes in the biologics landscape and their impact.

Summary

The market share of biological products as a percentage of overall drug products on the market is increasing, and it appears that the trend will continue. Biosimilars offer the health care system an opportunity to reduce costs and increase access to treatment options. Biosimilars must be positively perceived and adopted by numerous stakeholders to create and sustain a competitive landscape and effectively manage costs of care. However, efforts to ensure their safe and effective use, including pharmacovigilance and bidirectional communication, need to be prioritized to limit risks to patients and improve care. Ongoing collaboration with and education targeting a variety of stakeholders, including providers, patients,

payers, and policymakers, will be crucial for facilitating widespread use of these products and optimizing their value.

Biosimilar Resources

Academy of Managed Care Pharmacy Biosimilars Resource Center
https://www.biosimilarsresourcecenter.org

American Journal of Managed Care Biosimilars Resource Center
http://www.ajmc.com/essentials/biosimilars

ASHP Biosimilars Resource Center
http://www.ashp.org/menu/PracticePolicy/ResourceCenters/Emerging-Sciences/Biosimilars.aspx

FDA Information on Biosimilars
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/

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Judy Crespi-Lofton, MS, President, JCL Communications, Schwenksville, PA

Jann B. Skelton, BSPharm, MBA, President, Silver Pennies Consulting, Caldwell, NJ

APhA Biologics and Biosimilars Stakeholder Conference participants

Reginia Grayson Benjamin, BS, JD, Director of Legislative Affairs, Academy of Managed Care Pharmacy (AMCP)

Benjamin Bluml, BSPharm, Senior Vice President, Research and Innovation, American Pharmacists Association (APhA) Foundation

Mary Jo Carden, BSPharm, JD, Vice President, Government and Pharmacy Affairs, AMCP

Leah Christl, PhD, Associate Director for Therapeutic Biologics and Biosimilars, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration

John M. Coster, BSPharm, PhD, Director, Division of Pharmacy, Center for Medicaid and Child Health Insurance Program Services, Centers for Medicare and Medicaid Services

Barry D. Dickinson, PhD, Director, Science and Biotechnology, and Secretary, Council on Science and Public Health, American Medical Association

John Klimek, BSPharm, Senior Vice President, Standards and Information Technology, National Council for Prescription Drug Programs

Tom Koening, Executive Director, Biosimilar Market Access, Boehringer Ingelheim

Stacie Maass, BSPharm, JD, Senior Vice President, Pharmacy Practice and Government Affairs, APhA

Michael McShea, BSPharm, [second half of conference] Channel Strategy, Lilly USA

Josh Tomas O'Harra, [first half of conference] Assistant General Counsel, Managed Healthcare Services Legal, Lilly USA

Alan D. Ryan, BSPharm, MBA, Director, U.S. Advocacy and Alliance Development, Sandoz

James G. Stevenson, PharmD, FASHP, President, Hospital and Health Systems Services, Visante, and Professor, University of Michigan College of Pharmacy

Jaap Venema, PhD, Executive Vice President and Chief Science Officer, U.S. Pharmacopeial Convention

Kimberly Williams, PharmD, Director, Specialty Pharmacy Program, CareFirst BlueCross BlueShield