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# S U P P L E M E N T

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## NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives

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## Key Words

Biosimilars, follow-on biologics, health policy

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## Abstract

Biologics are essential to oncology care. As patents for older biologics begin to expire, the United States is developing an abbreviated regulatory process for the approval of similar biologics (biosimilars), which raises important considerations for the safe and appropriate incorporation of biosimilars into clinical practice for patients with cancer. The potential for biosimilars to reduce the cost of biologics, which are often high-cost components of oncology care, was the impetus behind the Biologics Price Competition and Innovation Act of 2009, a part of the 2010 Affordable Care Act. In March 2011, NCCN assembled a work group consisting of thought leaders from NCCN Member Institutions and other organizations, to provide guidance regarding the challenges health care providers and other key stakeholders face in incorporating biosimilars in health care practice. The work group identified challenges surrounding biosimilars, including health care provider knowledge, substitution practices, pharmacovigilance, naming and product tracking, coverage and reimbursement, use in off-label settings, and data requirements for approval. (*JNCCN* 2011;9[Suppl 4]:S1–S22)

## Executive Summary

The use of biologics is widespread and has become an essential element in cancer treatment and supportive care management; based on current patterns of drug development, the increased use of biologics in cancer is

inevitable. Patents for older biologics will soon expire, and the United States is developing a regulatory process for the approval of similar biologics (biosimilars). Therefore, the safe and appropriate incorporation of biosimilars into clinical practice for patients with cancer is important to consider. Biologics are complex to develop and manufacture, and therefore are often high-cost components of cancer treatment. The potential for biosimilars to provide cost competition and reduce the cost of biologics was the impetus behind the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), a part of the 2010 Affordable Care Act. As the FDA implements elements of the BPCI Act, stakeholders must actively engage in discussions to ensure biosimilars are safe and effective for the treatment of patients with cancer.

To provide guidance regarding the challenges health care providers and other key stakeholders face in incorporating biosimilars in health care practice, NCCN assembled a Work Group consisting of thought leaders from NCCN Member Institutions and other organizations external to NCCN. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government. The NCCN Biosimilars Work Group was convened in order to advise oncology practitioners and key stakeholders regarding challenges and recommendations concerning biosimilars in oncology. The

content of this White Paper represents the work of NCCN and may not necessarily reflect the opinions of the external work group members or the organizations with which they are affiliated.

### Incorporating Biosimilars Into Oncology Practice: Challenges in the United States

The NCCN Biosimilars Work Group recognized that substantial differences exist between biologics (i.e., drugs produced by living systems) and traditional small-molecule drugs (i.e., chemical drugs) in terms of basic chemical structure, molecular weight, and manufacturing processes. Generic small-molecule drugs can be replicated in an exact way so that they are atomically identical to their reference drug. Therefore, because generic versions of small-molecule drugs are completely identical, they can be manufactured, marketed, and used in clinical practice with relative ease compared with biosimilar products. However, be-

cause biologics are complex products produced by living systems, they will inherently exhibit some physiochemical differences in addition to the varying production processes that will also modify the products (e.g., purification methods), and therefore biosimilars can be close or “similar” to the innovator products but will not be identical. This can also occur with manufacturing separate lots of biologics, whether innovator or biosimilar, but is controlled for with tightly managed in-process controls. The science, regulatory processes, and pharmacovigilance mechanisms for these complex biologics are still developing. The fundamental differences between biosimilars and small-molecule generic drugs are key drivers of the identified challenges listed in Table 1.

### Key Recommendations

- Clinical trials are expected to be required, and, at minimum, these clinical trials should include

**Table 1 Challenges for Incorporating Biosimilars Into Oncology Practice in the United States**

Topic	Challenge, Consensus Statement, or Recommendation
Use of biosimilars for off-label indications	<ul style="list-style-type: none"> <li>• In oncology, the use of biologics for off-label indications is common.</li> <li>• Although the FDA is expected to determine whether the use of a biosimilar can be extrapolated to all labeled indications based on the data submitted, the challenge for clinicians, payors, and other stakeholders will be to decide whether the data (and therefore use of a biosimilar) can be extrapolated to off-label indications.</li> </ul>
Biosimilar economics and diffusion	<ul style="list-style-type: none"> <li>• Biosimilar development costs are relatively high (compared with small-molecule generics), and therefore on a percentage basis, cost savings from biosimilars may be more modest compared with small-molecule generic drugs.</li> <li>• However, because biologics are expensive therapies, any cost savings have the potential to be meaningful.</li> <li>• Questions exist for how biosimilars will be covered, reimbursed, and dealt with by United States payors. Additionally, coverage and reimbursement policies have the potential to positively or negatively affect patient access and uptake.</li> </ul>
Clinical trial enrollment	<ul style="list-style-type: none"> <li>• Potential barriers exist to enrolling patients in clinical trials for biosimilars.</li> <li>• For example, physician interest in enrolling patients in clinical trials involving biosimilars and patient interest in participating in these trials may be low.</li> </ul>
Biosimilar safety, product specific tracking, and naming	<ul style="list-style-type: none"> <li>• Pharmacovigilance will be important to show that biosimilars exhibit a comparable safety profile to the reference product.</li> <li>• Although many large institutions have the infrastructure to track the use of a specific product back to a given patient, this system is less common in community settings.</li> <li>• Therefore, in an environment in which multiple sources of individual biologic entities are available (i.e., multisourced environment), a particular challenge exists in tracking the source of a biologic administered in the community setting.</li> </ul>
Substitution practices	<ul style="list-style-type: none"> <li>• Differences in substitution practices may be seen between small-molecule drugs and their generic versions versus biologics and their corresponding biosimilars.</li> <li>• Substitution practices may vary among states but should only be considered if the FDA determines a biosimilar to be interchangeable with its corresponding biologic.</li> </ul>
Health care provider education	<ul style="list-style-type: none"> <li>• Preliminary data from an NCCN Trends Survey indicate that health care providers require education on biosimilars.</li> </ul>

clinical end points that are most sensitive to show a difference (if any difference does exist) between the reference and biosimilar products.

- The FDA should provide guidance as soon as possible to define “highly similar” quality attributes and “no clinically meaningful differences in efficacy and safety.”
- The NCCN Guidelines Panels should evaluate recommendations regarding the use of biosimilars where available. This will provide guidance to both institutional Pharmacy and Therapeutics (P&T) Committees and practitioners who do not routinely practice under the auspices of a P&T Committee (e.g., those in community practice).
- Biologics and biosimilars are complex, and education regarding the basic scientific principles about biologic manufacturing processes and pharmacovigilance efforts should be disseminated to health care practitioners, including physicians, pharmacists, nurses, and mid-level practitioners (e.g., physician assistants, nurse practitioners).

The NCCN Work Group consensus statements and recommendations are summarized in Tables 2 and 3.

## Overview and Background

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act. The Affordable Care Act contains the BPCI Act that establishes an abbreviated approval pathway for biological products that are shown to be “biosimilar” to, or further shown to be “interchangeable” with, an FDA-licensed biological product. The BPCI Act states that in order for a biologic product to be considered biosimilar to a reference product, the biological product must be proven to be biosimilar to a reference product based on data derived from analytical, animal, and clinical studies. The BPCI Act<sup>1</sup> defines “biosimilar” or “biosimilarity” as a 2-part demonstration that 1) the proposed biosimilar product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and 2) “no clinically meaningful differences” exist between the proposed similar product and the reference product in terms of “safety, purity, and potency.” Additionally, it must be proven that the proposed,

biosimilar product and reference product utilize the same mechanism or mechanisms of action for the

**Table 2 NCCN Biosimilars Work Group Consensus Statements**

Category	Consensus Statement
Importance, access, and affordability	<ul style="list-style-type: none"> <li>• The overall goal of biosimilars is to increase affordability and access to biologic medications for patients, which are often important therapies for cancer care.</li> <li>• The NCCN Work Group believes that biosimilars are important to oncology care, and is supportive of defining a biosimilars approval pathway (characterized in the Biologics Price Competition and Innovation Act of 2009).</li> </ul>
Approval pathway: demonstrate similarity	<ul style="list-style-type: none"> <li>• At the time of biosimilar approval, a biosimilar must have shown high similarity to the reference (i.e., innovator) product in quality attributes and pharmacodynamic and pharmacokinetic parameters.</li> <li>• Efficacy and safety of the biosimilar product must be comparable (i.e., no meaningful difference in safety and efficacy) to the reference product.</li> </ul>
Standardization with reference product	<ul style="list-style-type: none"> <li>• The NCCN Work Group agrees with current regulations that elements of a biosimilar drug product should follow the reference product (for the purpose of consistency of practice avoiding medication errors). For example, the dosing for a biosimilar agent should be the same as for the reference product. Additionally, Risk Evaluation and Mitigation Strategies (REMS) and the associated provider workflow process should be standardized between biosimilar and reference products.</li> </ul>
Tracking product use	<ul style="list-style-type: none"> <li>• The ability to track a patient’s receipt of a biosimilar product during routine clinical use down to the level of a specific manufacturer and batch was seen as a critical element of assessing and ensuring the safety of these medications.</li> </ul>
Need for education: patients and health care providers	<ul style="list-style-type: none"> <li>• Patients and health care providers require education to increase their understanding of biosimilars. Patients should also know all the medicines they receive.</li> <li>• In the context of multisourced biologics being available, this may help avoid medication errors if patients know the exact drug product they receive.</li> </ul>

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**Table 3 NCCN Biosimilars Work Group Recommendations**

Category	Recommendation
Approval pathway: use appropriate end points	<ul style="list-style-type: none"> <li>Clinical end points that are most sensitive to show a difference (if any difference does exist) between the reference and biosimilar products should be studied.</li> <li>Data regarding end points such as overall response, overall survival, and/or progression-free survival may be helpful for health care providers.</li> </ul>
Approval pathway: consistency and transparency	<ul style="list-style-type: none"> <li>A consistent approach and transparency in the FDA process is recommended to assess biosimilarity as defined by the law: 1) highly similar quality attributes, and 2) no meaningful differences in efficacy and safety.</li> <li>The required scientific data will be defined based on the known safety and efficacy profiles (i.e., risk/benefit ratio for the reference biologic).</li> </ul>
Biosimilars and the NCCN Guidelines Panels	<ul style="list-style-type: none"> <li>The NCCN Guidelines Panels should evaluate biosimilars and discuss their role in the context of the disease when appropriate, and provide specific recommendations regarding the use of biosimilars.</li> <li>The work group did not anticipate recommendations against biosimilars in NCCN Guidelines but felt that this information would be helpful to add clarity for clinicians, patients, and payors.</li> </ul>
Pharmacy & Therapeutics (P&T) Committee	<ul style="list-style-type: none"> <li>As with other drugs and biologics, an institution's P&amp;T Committee should review biosimilar products for use in their own specific patient population. This is a different approach from that used for generic small-molecule drugs.</li> <li>For practitioners who do not routinely practice under the auspices of a P&amp;T Committee (e.g., in community practice), consideration and review of individual biosimilar products (either informally or formally) should be instituted before routine use is implemented, as with other drugs and biologics.</li> </ul>
Need for education: health care practitioners and policy makers	<ul style="list-style-type: none"> <li>Biologics and biosimilars are complex, and education on the topic is usually provided in the context of the treatment of a specific disease. Therefore, more education regarding the basic scientific principles about biologic manufacturing processes and pharmacovigilance efforts should be disseminated to health care practitioners, including physicians, pharmacists, nurses, and mid-level practitioners (e.g., physician assistants, nurse practitioners).</li> <li>Additionally, this education should be disseminated to legislators and other policy-makers.</li> </ul>
Biosimilar safety, product specific tracking, and naming	<ul style="list-style-type: none"> <li>The FDA must provide guidance regarding the naming of biosimilars and whether they will have unique nonproprietary names.</li> </ul>

condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;

and the proposed biosimilar product have the same route of administration, dosage form, and strength as the reference product.<sup>1</sup>

The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act), which established an abbreviated pathway for the approval of generic drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The BPCI Act amends Section 351 the Public Health Service Act (PHSA) to add subsection (k), which establishes an abbreviated approval pathway for biosimilars. This creation of an abbreviated approval pathway under

the PHSA largely aligns with the Hatch-Waxman concept of permitting reliance for approval, at least partly, on an appropriate previously approved drug as the reference product, with the potential of saving time and resources and avoiding unnecessary duplication of human or animal testing. The implementation of an abbreviated approval pathway for biological products may present challenges given the scientific and technical complexities that may be associated with the larger and often more complex structure of biological products, and the processes through which these products are manufactured.

The policy issues surrounding biosimilars have come to the forefront of discussion because of biosimilars' potential to reduce health care costs. However, there are scientific and manufacturing challenges to ensuring that a biosimilar is "highly similar" to the innovator product. As of the drafting of this manuscript, the FDA has not released any guidances for



industry, raising questions about what will be necessary to gain FDA approval. Furthermore, because biosimilars will be new to the United States market, they present challenges to health care practitioners, who must be educated on the topic to make decisions about safe and appropriate use of biosimilars.

The development of biosimilars is anticipated to have a major impact on the management of cancer. The use of biologics is widespread and has become an essential component in cancer treatment and supportive care management. Given the current development of new biologics in cancer, the use of biologics will clearly increase. Patents for older cancer biologics will soon expire, removing one of the barriers to commercialization of biosimilars. The potential to provide wider access to more affordable cancer biologics may be realized through the BPCI Act; however, the regulatory process for the approval of biosimilars is under development by the FDA. As the FDA implements elements of the BPCI Act, stakeholders must actively engage in discussions to ensure that biosimilars are safe and effective for the treatment of patients with cancer.

### Biosimilar Versus Interchangeable Drugs

A biosimilar may be shown to be highly similar to a reference product based on data derived from analytical, animal, and clinical studies. Minor differences are allowed in clinically inactive components as long as no clinically meaningful differences exist between the proposed biosimilar and the reference product with regard to safety, purity, and potency (presumably pharmacokinetics, pharmacodynamics, clinical safety, and efficacy). Requirements to meet the “no clinically meaningful differences” standard have not been defined in the law, and, depending on FDA’s implementation of the biosimilar approval pathway, may be variable among products based on the known safety and efficacy profile of the reference products.

The BPCI Act also establishes that biosimilars may be further determined to be interchangeable products. To be deemed interchangeable with the reference product, the biosimilar is expected to produce the same clinical results in any given patient. The law also defines interchangeable to mean “that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

For biologics that are administered more than once to a patient, the risks in terms of safety and efficacy of alternating or switching between use of the reference product and biosimilar must be equal to the risk of using only the reference product. However, methods for adequate switching/alternating studies have not yet been defined.

### Acceptance of Biosimilars

Ultimately, physicians, pharmacists, payors, and others will influence the uptake and diffusion of biosimilars into clinical practice. Oncologists will need to be confident in the data used to support FDA approval of biosimilars, both in terms of biosimilarity and the potential for interchangeability as assessed and communicated by the FDA.

Cancer is often catastrophic and complex to treat, and therefore, before prescribing a biosimilar, oncologists must have the utmost confidence in the data supporting biosimilar approval. Also, efficacy and safety, including immunogenicity profiles of the biosimilar and reference biologic, will need to be examined before most oncologists will prescribe a biosimilar. Because of the widespread accepted use of biologics off-label in oncology (such as use guided by the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] and other guidelines), oncologists will likely extrapolate data for FDA-approved indications to off-label uses.

### Regulation Experience in the European Union

Biosimilars are already established in the European Union (EU). The EU established a legal pathway starting in 2004, before many biologics started coming off patent. To date, 4 companies have successfully developed and received approval for biosimilars to be marketed in the EU. EU regulators began using the term “biosimilars” (“similar biological medicinal products”) to describe the biopharmaceuticals produced to closely replicate existing biologic drugs, and also developed a regulatory approval pathway for biosimilars beginning in 2005. The European Medicines Agency (EMA) oversees the authorization of biosimilars in the entire EU, much as the FDA does in the United States based on the BPCI Act.<sup>2,3</sup> The following section explores the EMA experience with

biosimilars, including interchangeability and substitution; marketing authorization; extrapolation of data; and safety.

As noted by Mellstedt et al.,<sup>4</sup> the EMA approach to biosimilars is based on the idea that, "...biosimilars are not generic equivalents of the innovator products." The EMA provides the following description of biosimilar medicine:

"...a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."<sup>5</sup>

As noted in the above description, health care professionals decide the interchangeability of a biologic reference medicine and the biosimilar; the individual member state control automatic substitution, not the EMA. Several EU member nations have passed measures prohibiting or restricting automatic substitution of biosimilars for innovator biologics at the hospital or pharmacy level.<sup>2,3</sup> In the United States, interchangeability of a biosimilar is determined by the FDA per the BPCI Act. Substitution practices with regard to drug products have been historically guided by state laws and State Pharmacy Boards.

Marketing authorization can be acquired in the EU once the EMA has approved a biosimilar for safety, efficacy, and quality.<sup>5</sup> These standards are governed by the EMA's Committee for Human Medicinal Products (CHMP), which defines the required purity of the biosimilar; requirements for clinical safety and efficacy, nonclinical studies, and clinical trials, which must demonstrate pharmacodynamic and pharmacokinetic properties; and drug class-specific guidelines for select biosimilars, with varying requirements for clinical trials. Seven biosimilar molecules have been approved under 14 different marketing applications in Europe, whereas 5 products were withdrawn or rejected by the EMA. Biosimilar erythropoiesis-stimulating agents (ESA), myeloid growth factors, and somatotropins are currently available in the European

market.<sup>2,6</sup> The EMA is expected to finalize its guideline on requirements for biosimilar products containing monoclonal antibodies in 2011.<sup>7</sup>

The EMA also allows for extrapolation of data, if properly justified, for use of biosimilars in indications that were not formally studied. Additionally, because of rare serious adverse effects, postapproval pharmacovigilance and monitoring of immunogenicity are required based on the known safety profile of the reference product.<sup>4</sup>

The aforementioned experience in the EU will be useful for developing policy on biosimilars in the United States. However, differences between the EU and United States health care systems will translate into some differences in how the United States will incorporate biosimilars into practice.

## WHO Guidance on Biosimilars

The WHO, the public health arm of the United Nations, developed guidance for biosimilars through its Expert Committee on Biological Standardization (ECBS), which issued its finalized, "Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)" in April 2010. The guidelines are meant

...to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier.<sup>3,8</sup>

These guidelines are a relevant resource for nations that have not yet established a standard for integrating biosimilars into practice, and are similar to EMA guidance on establishing biosimilarity.<sup>3</sup> Furthermore, the WHO guidance may be useful in less strictly regulated markets (e.g., China and India) where copied biopharmaceuticals have already been in use for many years.<sup>2</sup>

It is important to distinguish biosimilars approved in highly regulated environments from biologic products in less-regulated environments. One author has referred to biologic products on the market in areas of the world with limited regulations as "biopharmaceuticals not subject to regulatory approval" (B-NSRA) products.<sup>9</sup>

## Biosimilars in the United States

Although the BPCI Act was passed in 2010, many details of the United States biosimilar approval process are not yet clear. In 2011, the FDA is expected to release guidance to further define the United States biosimilar approval process as established by the BPCI Act. The pending biosimilar guidance is expected to provide important perspective on current FDA thinking on biosimilars and improve the transparency of the process for biosimilar approval. However, the BPCI Act allows sponsors to submit applications without guidance, and therefore biosimilar sponsors could submit an application at any time.

Before the BPCI Act, United States law did not provide an abbreviated approval process for non-innovator biologics approved under the PHSA. The pathway for abbreviated approval of generic small-molecule drugs provided by the Hatch-Waxman Act did not apply to those biologics. The Hatch-Waxman Act amended the FD&C Act to provide for a generic pathway for only those drug products subject to approval under the FD&C Act. Most biologics are subject to the approval pathway under section 351 of the PHSA, and therefore the Hatch-Waxman generic approval pathway does not apply.<sup>10</sup> A few simple biologic drugs, such as human growth hormones and insulin, are exceptions to this rule, because they have been approved under the FD&C Act.<sup>11</sup>

Several developments have made the introduction of biosimilars imminent in the next several years in the United States. Although details of the abbreviated pathway for biosimilar approval are still emerging, legislation that develops the framework of the regulatory process has removed an important legal barrier to the introduction of biosimilars in the United States. Furthermore, patents will soon expire on many biologic products commonly used in the treatment of patients with cancer (Table 4). As the introduction of biosimilars for these patients nears, clinicians must be well informed to understand the appropriate application of all biologics (reference products and biosimilars) in their practice setting.

## Work Group Description

To describe potential challenges for incorporating biosimilars into clinical practice and to offer recommendations and guidance to relevant stakeholders, NCCN convened a Work Group comprising thought

leaders from NCCN Member Institutions and other organizations external to NCCN. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government. The work group included representatives from both academic centers and the community practice setting. The NCCN Work Group meeting was held on March 12, 2011, during the 2011 NCCN 16th Annual Conference in Hollywood, Florida. In addition, NCCN conducted an Oncology Policy Summit: Biosimilars – Regulatory, Scientific, and Patient Safety Perspectives held on April 29, 2011, in Washington, DC. This summit included additional thought leaders representing the aforementioned groups and other relevant stakeholders.

The overall objective of the work group was to identify issues related to biosimilars that health care providers who care for patients with cancer will encounter. Because regulations are emerging, some discussion of the regulatory aspects of biosimilars occurred, but the focus remained on implications of biosimilars in the care of patients with cancer.

Additionally, the work group realized the need to collect data regarding provider knowledge, educational needs, and planned use of biosimilars. Therefore, the NCCN Work Group developed a survey that was administered through the NCCN Trends Surveys and Data program. These survey data were presented at the NCCN Oncology Policy Summit: Biosimilars – Regulatory, Scientific, and Patient Safety Perspectives.

This document encapsulates the discussion during the work group meeting and at the policy summit, including background on biologics, identified

**Table 4** Sample of Important Biologics in Oncology and Their United States Approval Dates

Biologic	FDA Approval
Bevacizumab (Avastin)	February 6, 2004
Cetuximab (Erbix)	February 12, 2004
Darbepoetin alfa (Aranesp)	September 17, 2001
Epoetin alfa (Epogen/Procrit)	June 1, 1989
Filgrastim (Neupogen)	February 20, 1991
Pegfilgrastim (Neulasta)	January 31, 2002
Rituximab (Rituxan)	November 26, 1997
Trastuzumab (Herceptin)	September 25, 1998

Data from U.S. Food and Drug Administration Web site. Available at: <http://www.fda.gov/>. Accessed August 5, 2011.

challenges to incorporating biosimilars into oncology practice from a health care provider's perspective, and a descriptive analysis of the data obtained from the NCCN Trends Survey. Finally, this document outlines the consensus statements and recommendations offered by the NCCN Work Group.

## Biologics and Biosimilars in Oncology

Although the use of biologics encompasses many specialties of medicine, biologics have made a major impact in the medical management of cancer. Biologics have improved clinical outcomes (including overall survival) and are integral for supportive care management of symptoms caused by cancer or chemotherapy. Biologics are essential in most NCCN Guidelines, including breast, colorectal, esophageal, gastric, head and neck, kidney, and non-small cell lung cancers, in addition to Hodgkin and non-Hodgkin's lymphoma (B-cell lymphoma, Burkitt lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, gastric mucosa-associated lymphoid tissue [MALT], lymphoblastic lymphoma, mantle cell lymphoma, non-gastric MALT, primary cutaneous B-cell lymphoma, and splenic marginal zone lymphoma). They are also vital in the treatment of cancer and chemotherapy-induced anemia and neutropenia according to the NCCN Supportive Care Guidelines. To view the most recent version of these guidelines, visit the NCCN Web site at [www.NCCN.org](http://www.NCCN.org).

A significant early example is rituximab, an anti-CD20 monoclonal antibody that was initially approved by the FDA in 1997 for the treatment of relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma.<sup>12</sup> Since its approval, numerous studies have shown rituximab to be beneficial in numerous types of B-cell lymphomas, including diffuse large B-cell lymphoma, in which multiple independent studies have shown that its addition to standard chemotherapy prolongs survival.<sup>13</sup> Trastuzumab is another example of a successful biologic for the active treatment of cancer. Studies have shown favorable outcomes with trastuzumab in terms of improved overall survival in patients with HER2-positive breast cancer.<sup>14</sup> Myeloid growth factors (e.g., pegfilgrastim, filgrastim), also biologics, play an important role in the supportive care management of symptoms caused by cancer or chemotherapy. In

particular, myeloid growth factors have benefited patients through managing chemotherapy-related neutropenia in a wide range of tumor types.<sup>15</sup>

## Economics of Biosimilars

Of the 199 individual agents listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium), only 15% are classified as biologics. Despite the relatively small number of biologics in the NCCN Compendium, biologics account for most of the total oncology-related drug expenditures in outpatient clinics.<sup>16</sup> Recent drug expenditure data provided by Doloresco et al.<sup>16</sup> show the top antineoplastic drugs (i.e., drugs for the active treatment of cancer) on which outpatient clinics spent the most money in 2010; 5 of the top 20 are biologics (Table 5), and biologics constituted the top 3 expenditures (bevacizumab, rituximab, and trastuzumab). Collectively, biologics accounted for more than half (55%) of the total expenditures of the list of top 20 drugs (Figure 1). These data underestimate the proportion of total expenditures for all biologics in oncology care, because drugs for the supportive care management of cancer- or chemotherapy-related symptoms (e.g., epoetin alfa, darbepoetin, filgrastim, pegfilgrastim) are not reported in this study.

According to the previously described definition of "biosimilar," patients who receive biosimilars would fare no better or worse clinically than if they had received the originator biologic, leading some to question the need for biosimilars. Given that biologics for patients with cancer can be expensive, biosimilars may present an opportunity to improve patient access through providing lower-cost options without compromising patient outcomes.

Previous experience with generics for small-molecule drugs offered price reductions up to 80% compared with their branded counterparts.<sup>17</sup> Furthermore, a report by the Generic Pharmaceutical Association indicates that the use of generics saved the United States health care system an estimated \$824 billion during the previous decade.<sup>18</sup> However, biosimilars have a different economic paradigm. Because of higher development, facility, and manufacturing costs, biosimilar savings are expected to be more modest. A Congressional Budget Office estimate suggested a discount of up to 40%.<sup>19</sup> In the EU, ESA biosimilars confer an estimated 25% to 30% cost savings compared with their innovator products, which also led to a decrease in innovator

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**Table 5 Top 20 Antineoplastic Drug Expenditures in Outpatient Clinics**

Rank	Drug	Biologic or Nonbiologic	2010 Total Expenditure (in Millions of Dollars)	Top 20 Total (%)
1	Bevacizumab	Biologic	1884	22.1%
2	Rituximab	Biologic	1466	17.2%
3	Trastuzumab	Biologic	931	10.9%
4	Docetaxel	Nonbiologic	688	8.1%
5	Pemetrexed	Nonbiologic	579	6.8%
6	Oxaliplatin	Nonbiologic	508	6.0%
7	Gemcitabine	Nonbiologic	463	5.4%
8	Cetuximab	Biologic	329	3.9%
9	Bortezomib	Nonbiologic	327	3.8%
10	Leuprolide	Nonbiologic	220	2.6%
11	Paclitaxel–albumin	Nonbiologic	212	2.5%
12	Bendamustine	Nonbiologic	208	2.4%
13	Azacitidine	Nonbiologic	148	1.7%
14	Liposomal doxorubicin	Nonbiologic	130	1.5%
15	Decitabine	Nonbiologic	92	1.1%
16	Topotecan	Nonbiologic	86	1.0%
17	Fulvestrant	Nonbiologic	81	0.9%
18	Panitumumab	Biologic	70	0.8%
19	Ixabepilone	Nonbiologic	60	0.7%
20	Temsirolimus	Nonbiologic	48	0.6%
		Total of Top 20	8528	100.0%

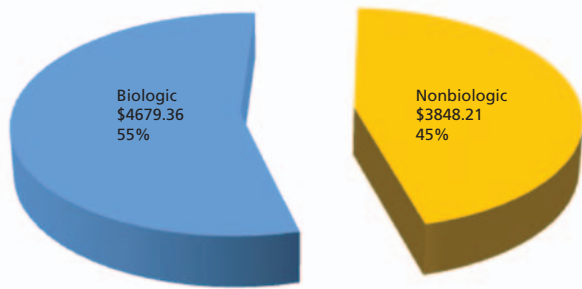
Adapted from Doloresco F, Fominaya C, Schumock GT, et al. Projecting future drug expenditures—2011. *Am J Health Syst Pharm* 2011;68:929; with permission.

ESA prices.<sup>2</sup> Mellstedt et al.<sup>4</sup> note that although cost savings for biosimilars will not be as great as for small-molecule generics, this should continue to increase access to biologic drugs in the EU.

Pending FDA data requirements for the established biosimilar pathway will have an effect on the cost of biosimilars, contingent on the level of data needed to establish biosimilarity, which could in turn affect patient access to these drugs. If data requirements are substantial, fewer biosimilars may be able to come to market because of associated higher clinical trial costs, and may have a lesser impact on potential cost savings. Alternatively, fewer data requirements could allow more biosimilars to come to market and may subsequently cause a greater impact on potential cost savings, but also greater uncertainty regarding the comparability of the biosimilars' clinical safety and efficacy.

Because economics will play an important role in the introduction of biosimilars into practice in the United States, policies and regulations should be in

place to ensure that 1) a biosimilar product is “highly similar” to the reference product, and 2) systems are established to identify and mitigate any unintended consequences. NCCN challenged the Biosimilars Work Group with identifying the challenges of incorporating biosimilars into oncology practice (from the perspective of health care practitioners when caring for patients) and to subsequently offer recommendations to address those challenges. During early discussions of the work group, participants noted that one of the root causes of the challenges identified by the work group revolved around the differences between biologics and traditional small-molecule chemical entities. Specifically, the scientific principles surrounding the development of “copies” of the reference product (i.e., “biosimilars” for biologics and “generics” for small-molecule drugs) for these distinct classes of drugs are substantially different, and thus require further discussion before describing the challenges identified by the work group.



**Figure 1** Biologics vs. nonbiologics distribution of drug expenditures of the top 20 antineoplastic drugs in outpatient clinics (in millions of dollars). Data from Doloresco F, Fominaya C, Schumock GT, et al. Projecting future drug expenditures – 2011. *Am J Health Syst Pharm* 2011;68:921–932.

### Biosimilars Versus Small-Molecule Generics

The differences between biosimilars and generics for small-molecule drugs relate to the chemical differences between their respective reference products (Table 6); biologics are far more complex than traditional small-molecule drugs. Biologics are “products of biotechnological origin that contain proteins derived from DNA technology and hybridoma techniques,” and use living organisms (e.g., bacteria, yeasts, vi-

ruses, other animal cells) as part of the production process.<sup>20</sup> Figure 2 provides more detail on the production of biologics. However, small-molecule drugs are relatively simple in structure and are mainly synthesized through organic chemistry reactions.

The basic building blocks of biologics are glycoproteins (i.e., amino acids and sugar molecules), which transcends the basic atomic unit for small-molecule drugs. These amino acid building blocks are strung together in a specified sequence to form its primary structure (i.e., its amino acid sequence). Although this sequence is very important for the protein’s function, one cannot discount the influence of the secondary, tertiary, and quaternary structures toward its therapeutic function. Therefore, even small changes in the folding of the protein can manifest into a clinically meaningful difference in efficacy or toxicity. Moreover, the glycosylation pattern of a biologic contributes to its clinical profile. Changes in the pattern of glycosylation can occur based on the cells in which the drug is produced and their intricate, multistep manufacturing process,<sup>21–23</sup> and these alterations in glycosylation patterns could also alter clinical outcomes.

Small-molecule generics, however, are structurally much simpler and generally not sensitive to process

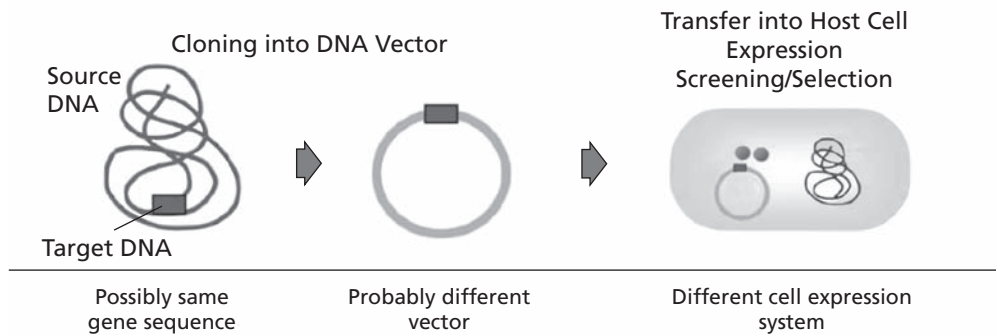
**Table 6 Summary of Key Differences Between How Biosimilars and Small-Molecule Generics Compare With Their Respective Reference Product**

Area		Biosimilars	Small-Molecule Generics
Product	Chemical structure	The amino acid sequence is the same, but there is expected to be slight differences in terms of protein folding and glycosylation	The active drug is chemically identical to the reference product
	Analytical characterization	The final structure cannot be fully defined based on current analytical techniques; therefore, the degree of structural similarity to the reference product is unknown	Current techniques are available to ensure that the active drug in the generic product is identical to the reference product
Manufacturing	Complexity	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product	Relatively simple, uses organic medicinal chemistry reactions
	Impact of a change in manufacturing process	Small changes in process may alter the final structure and function of the protein	Likely to be negligible because the end product is identical
Regulation	Legislation approving an abbreviated pathway	The Biologics Price Competition and Innovation Act of 2009 establishes framework for an abbreviated approval pathway for biosimilars; guidance yet to be released by the FDA	Hatch-Waxman Act allows generics to be approved through an Abbreviated New Drug Application (ANDA)

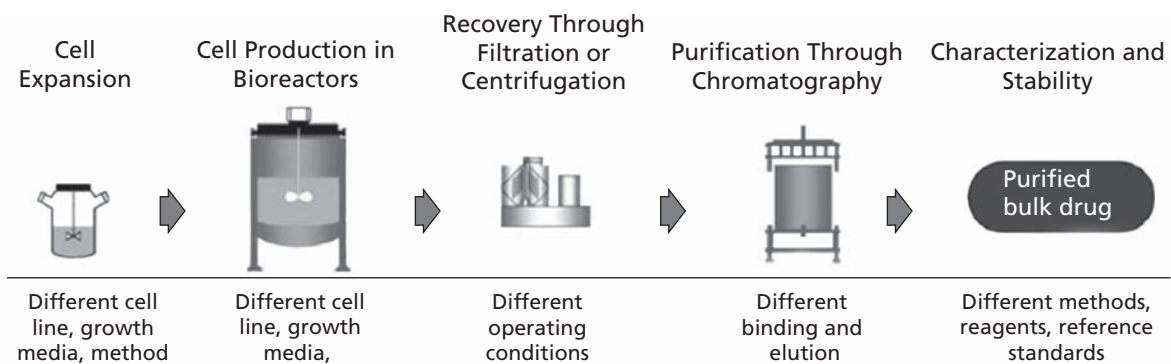
Data from Nowicki M. Basic Facts about Biosimilars. *Kidney Blood Press Res* 2007;30:267–272; and Kuhlmann M, Covic A. The protein science of biosimilars. *Nephrol Dial Transplant* 2006;21(Suppl 5):v4–v8.

## Regulatory, Scientific, and Patient Safety Perspectives

## Cloning and Protein Expression



## Protein Production, Purification, and Validation



**Figure 2** Biologics manufacturing process.

From Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol* 2008;19:412–419; by permission of Oxford University Press.

changes. The basic atomic units (e.g., carbon, oxygen, hydrogen, nitrogen) that form the chemical structure of the completed molecule can be fully characterized using current technology to ensure that it is identical to the active drug in the reference product. Thus, if the active component of a generic drug can be shown to be completely identical to the reference product, the actual process for synthesizing it is of less concern.

Unlike generic small-molecule drugs, biosimilars will not be identical to the reference product because of differences in the cell lines of each manufacturer and in their different manufacturing processes; the complex process for manufacturing the reference biologic is often proprietary. Furthermore, the analytical technology currently available cannot fully characterize a protein's 3-dimensional structure.<sup>21</sup> Different lots of any biologic product manufactured by the same process are not 100% identical. Therefore, demonstrating analytically that a biosimilar is highly similar to its reference product and showing that any small differences in the molecule compari-

son do not have any clinically meaningful differences is a practical and appropriate policy, because it is applied to monitor various lots of any biologic product. Previous discussions have already established that this should be determined through assessments of quality, efficacy, and safety, using analytical, preclinical, clinical, and postmarketing surveillance studies to achieve this goal.<sup>23</sup>

These fundamental differences between biosimilars and generic small-molecule drugs warrant a paradigm shift in the thinking of all stakeholders (e.g., patients, health care practitioners, innovator and biosimilar manufacturers, payors, and government agencies) when dealing with these products; biosimilars must not be considered simply "generic biologics."

Additionally, stakeholders must come to a consensus to determine biosimilar policies that strike the right balance between the following competing benefits: innovation, access to medications, affordability, safety/efficacy, and availability of data. Com-

peting interests exist among these core values; some values are supported by stricter policies and regulations, whereas other values are supported by more lenient ones (Table 7). A key example is the amount of data required for approval. If the amount of safety and efficacy data required for approval is too large, biosimilar development costs will be so high that few products will reach the market, and cost reductions will be limited. However, more limited data requirements for biosimilar approval will lead to potentially greater reductions in biosimilar costs, but uncertainty of clinical comparability for safety and efficacy will increase when fewer data are provided. Defining the appropriate balance in this debate may be challenging, and different stakeholders naturally will gravitate toward opposite ends of the spectrum.

Additionally, many of the challenges stakeholders face when dealing with biosimilars are not unique to these products. These challenges with all biologics (reference products and biosimilars) highlight some of the system complexities within the current United States health care system, further demonstrating that a better system would obviate the need for some of the recommendations stated in this document.

### Incorporating Biosimilars Into Oncology Practice: Challenges in the United States

During the NCCN Biosimilars Work Group meeting and the NCCN Oncology Policy Summit, many challenges were identified for integrating biosimilars into oncology clinical practice, which can be divid-

**Table 7 Competing Interests in Key Values for Biosimilars in Oncology**

<b>Supports Stricter Policies and Regulations</b>	<b>vs.</b>	<b>Supports More Lenient Policies and Regulations</b>
Preservation of innovation to develop new treatments and cures	vs.	Broader access to medications
Data ensuring safety and efficacy	vs.	Affordability
Availability of data in a wide variety of indications	vs.	Extrapolate clinical utility from "key" efficacy data

Sound health care policy is a compromise between discovery of new medicines and broader or lower-cost access to existing ones without compromise in patient safety or efficacy.

ed into 6 broad categories: 1) use of biosimilars for off-label indications; 2) biosimilar economics and diffusion; 3) clinical trial enrollment; 4) biosimilar safety, product-specific tracking, and naming; 5) substitution practices; and 6) health care provider education. Table 1 further summarizes these challenges and offers additional detail. NCCN Work Group consensus statements and recommendations regarding these challenges are presented later.

#### Off-Label Indications

Oncology drugs are frequently prescribed for indications other than what is listed in the FDA label, and this approach is appropriate in many situations.<sup>24</sup> Therefore, substantial discussion at the Policy Summit centered on the use of biosimilars for off-label indications, including data requirements for extrapolation. Off-label use is generally driven by published clinical experience that is insufficient for regulatory approval. For example, a recent study using a claims database found an off-label prescribing rate of 25% for rituximab.<sup>25</sup> When biosimilars are introduced into the United States market, they are anticipated to carry labeled indications that are equal to (or perhaps more narrow than) the label of the reference product. However, the exact labeling will depend on the data package submitted to the FDA by the biosimilar manufacturers. Controversy exists about when it is clinically appropriate to extrapolate data obtained from the reference molecule to the biosimilar (i.e., when the biosimilar has never been tested in a particular clinical condition).

Overall, it seems that payors will prompt the use of biosimilars, but how the off-label prescribing of biosimilars will be interpreted by payors is uncertain. If the decision to use a biosimilar for an off-label indication is based on an extrapolation of data (and not on direct evidence), payors may decide that data are insufficient to justify payment for its use in that indication, and reimbursement will not occur. Conversely, an insurer may decide they will only reimburse for the biosimilar and not the originator biologic in that off-label setting, despite the lack of evidence proving safety and effectiveness, largely because of cost savings.

#### Biosimilar Safety, Product-Specific Tracking, and Naming

Because of the complexity of biologic development and production and the slight differences that will exist between biologics and biosimilars, some concern



exists that adverse events unique to biosimilars may appear. Potential safety concerns regarding biosimilars prompted discussion of the need to track and retrieve data on the use of biosimilars. To determine if different adverse event profiles exist, adequate mechanisms for tracing and determining if a patient received the reference biologic or the biosimilar are needed.

A widely discussed approach to biosimilar tracking is to assign biosimilars a related, but unique and distinguishable, nonproprietary name compared with the reference product. Proponents of this strategy maintain that this is the most straightforward way to collect postmarket safety and efficacy data, track adverse events, and correctly attribute these events to the specific biologic source. Additionally, different names would prevent unintentional substitution of one product over another. Some contend that the current international rules governing naming (i.e., the International Nonproprietary Name [INN] system), first developed in 1950 by the WHO, are more correctly suited for small-molecule chemical substances that have an identical molecular structure, although they have since been adapted to address biologics.<sup>26,27</sup> The INN program's mandate is to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products."<sup>28</sup>

In the United States, nonproprietary names for all pharmaceuticals are approved through the United States Adopted Names Council (USANC). The USANC is trisponsored by the American Medical Association (AMA), the United States Pharmacopoeial Convention (USP), and the American Pharmacists Association (APhA), and the FDA cooperates with and is represented on the USANC. The United States Adopted Names (USAN) program states that its goal is to select "simple, informative, and unique nonproprietary names [also called *generic names*] for drugs by establishing logical nomenclature classifications based on pharmacologic and/or chemical relationships."<sup>29</sup> The USANC retains authority over drug names in the United States but also works to harmonize drug names across the world. The USANC's international efforts include working with the WHO INN Expert Committee and other national nomenclature groups to standardize drug nomenclature and establish rules governing the classification of new substances worldwide.

The process for obtaining an USAN starts with the manufacturer completing an application. Two

important requirements for applying are that the substance has entered clinical trials and has an Investigational New Drug (IND) number from the FDA. The manufacturer may suggest a name or names based on current nomenclature practices. These practices involve the adoption of standardized syllables called *stems* that relate new chemical entities to existing drug families. Stems may be prefixes, suffixes, or infixes in the nonproprietary name. Each stem can emphasize a specific chemical structure type, a pharmacologic property, or a combination of these attributes. The recommended list of USAN stems is updated regularly to accommodate drugs with new chemical and pharmacologic properties. After initial review by USANC staff, the USANC recommends and the sponsor accepts a name after the balloting process is complete. When considering an acceptable name, the following criteria are constantly kept in mind by the USANC: usefulness to health care providers, patient safety, adherence to the nomenclature rules, absence of conflicts with existing names, suitability for use internationally, ease of pronunciation, and other factors.

At the completion of the USANC review and after a name is accepted, the USANC Secretariat submits it to the INN Expert Group for consideration, additional trademark clearance, and linguistic evaluation on behalf of the sponsor (depending on the type of submission). The INN Expert Group evaluates suggested names following procedures somewhat similar to those of the USAN Council; however, the deliberation and actual name selection occurs at each of their biannual meetings, not through a year-round balloting process. Many firms seeking a USAN are multinational companies with subsidiaries outside the United States. It is highly desirable to the drug firms, the various nomenclature committees, and the medical community that a global name be established for each new substance. To prevent confusion with the use of multiple nonproprietary names in different countries, the WHO-INN Program coordinates drug nomenclature internationally.<sup>30</sup>

Small-molecule generic manufacturers do not need to go through the USAN process because their products are identical to the innovator, and the generic drug will automatically have the same nonproprietary name as the innovator. Because biosimilars are not identical to the innovator biologic,

USAN has stated that they cannot assume they will have the same nonproprietary name. Therefore, the FDA must provide a decision declaring whether biosimilars and innovator biologics will share nonproprietary names, which will allow biosimilar manufacturers to move forward with naming their products.

The WHO, which coordinates the INN Program, advises that biosimilars should have a unique brand name, but recommends against unique INNs to identify nonglycosylated biosimilars, noting that INNs should not be relied on alone to determine interchangeability of biosimilars with biologic reference products. The authority to decide interchangeability and substitution rests with National Regulatory Authorities (NRAs). Additionally, the WHO recommends the use of lot numbers to ensure traceability.<sup>3</sup> However, in the case of naming epoetins and other glycoproteins, both reference products and biosimilars, the WHO recommended that amino acid differences should be denoted with prefixes in the INN name, and that glycosylation differences should be indicated by unique Greek letters (e.g., epoetin  $\alpha$ , epoetin  $\beta$ ).<sup>2</sup> Although WHO recommendations regarding the naming of biosimilars have provided the basis for global naming practices, they have not been applied with consistency worldwide for epoetin products.

A major disadvantage of unique naming of biosimilars is the potential confusion regarding comparability of the biosimilar to the reference product; clinicians and patients may interpret different names to mean that the products do not have similar efficacy and safety, even if regulatory agencies have determined that they meet biosimilarity requirements. Confusion of drug names has been frequently cited as a cause of medication errors.<sup>31,32</sup> Regarding biosimilars, unique names could cause confusion among prescribers, which may lead to prescribing errors that would have a limited risk of adverse events. However, a similar or related name with the same root but a small difference in prefix or suffix could represent that it is a similar molecule and simply identify a unique manufacturer of the specific product. This is now the approved practice in Japan for biosimilar products.

Hennessy et al.<sup>26</sup> evaluated the options for tracking reference biologics and biosimilars to conduct postapproval surveillance and pharmacovigilance.

Several potential options were proposed, including,

- 1) Assign different nonproprietary names to biosimilar and innovator compounds...
- 2) Develop different HCPCS [Healthcare Common Procedure Coding System] codes for biosimilar products that share the same nonproprietary name...
- 3) Shift billing for physician-administered products from HCPCS codes to NDCs [National Drug Codes]...
- 4) Establish prospective registries linked to electronic health data...[and]
- 5) Ensure that particular providers exclusively use a particular version of a biological product.

The working group discussed that an alternative means of tracking biosimilars for safety purposes would be to use NDCs, and that the lot number could be used for pharmacovigilance purposes. A concern was raised that current technology systems (e.g., electronic health records) and institutions/practices are not uniform in the capability or ability to track this information on a point-of-care basis. However, this is the method used for tracking small-molecule generics, although those are generally dispensed in outpatient pharmacies. Importantly, NDC codes are not always reported back to the prescribing physician once the patient picks up the prescription from a retail pharmacy. The feedback loop would need to be closed to make the use of NDCs for tracking possible. Also, if more than one biosimilar is available, a physician would not know the manufacturer of the drug their patient received without receiving feedback from the pharmacy. Many patients may also be unaware that information such as NDCs is available on the packaging of their medications, and of the possible use of NDCs for reporting events.

### Substitution Practices

Laws and regulations governing the practice of substituting biosimilars for reference biologics will need to be fully elucidated, and this area could become very complex for clinicians. Consistent with longstanding practice regarding drug products approved under the FD&C Act, the BPCI Act allows the FDA to make an interchangeability determination. The practice of automatic drug substitution, which is when the pharmacist substitutes a generic product for the brand product unless the prescriber specifies otherwise, is governed by state law and state boards of pharmacy. However, current state substitution laws were drafted and enacted long ago, and the concepts of a biosimi-

lar and an interchangeable biosimilar are new. The possibility exists that individual states could develop laws or regulations that would influence the use and substitution of biosimilars, and these laws may or may not take into account the interchangeability determination made by the FDA. Although unclear based on the limited information available to date, the approach to biosimilar substitution could vary widely among states, which could further confuse clinicians.

Additionally, substitution laws and practices may not be relevant in hospitals and other settings with a P&T Committee. In these settings, therapeutic interchange practices can be established, which provides flexibility for each organization to establish their preferred agents. (*Therapeutic interchange* is defined as the dispensing of a drug that is therapeutically equivalent to but chemically different from the drug originally prescribed by a physician or other authorized prescriber).<sup>33</sup> How many biosimilars will seek and obtain an FDA interchangeability determination and whether states will establish specific biosimilar substitution laws is currently unclear. However, developments in this area clearly will have an important influence on the practical application of biosimilars, and clinicians should carefully monitor developments in this area.

### Health Care Provider Education

Because the practitioners are the ones who will ultimately prescribe, dispense, and administer these agents, provider knowledge regarding the differences in science and regulation between biosimilars and generic small molecules is of utmost importance. Currently, provider knowledge about this topic is suboptimal, as supported by preliminary data obtained by an NCCN Trends Survey, which are subsequently described. Appropriate education should be provided as this area develops further. Additionally, once naming conventions for biosimilars have been established by the FDA, specific education on biosimilar names should be provided.

### NCCN Trends Survey Results

To gather initial baseline data about clinicians' knowledge and perceptions about biosimilars in oncology, the NCCN Work Group developed a survey to collect this information. This survey is one of the first to document oncology practitioners' knowledge and opinions regarding biosimilars. The 4-question survey was made available to attendees at the NCCN 16th

Annual Conference and was administered on March 10 and 11, 2011. The survey questions were on the topics of familiarity with biosimilars legislation, interest in using biosimilars in practice, and importance of various types of data surrounding biosimilar products. The survey also asked participants to anticipate their future approach to using biosimilars for specific biologics (e.g., ESAs, myeloid growth factors).

The survey results are presented in this report as descriptive statistics of the aggregate data. When appropriate, further analysis of the data in the form of splitting the data by provider type (e.g., physician, nurse, pharmacist) and familiarity with biosimilars legislation (i.e., survey question number 1) is described.

A convenience sample of 277 conference attendees responded to the survey. Respondent demographics are depicted in Table 8. Most respondents were physicians (n = 129), followed by nurses (n = 71) and pharmacists (n = 38). Other types of clinicians or nonpracticing clinicians also responded to the survey (n = 39).

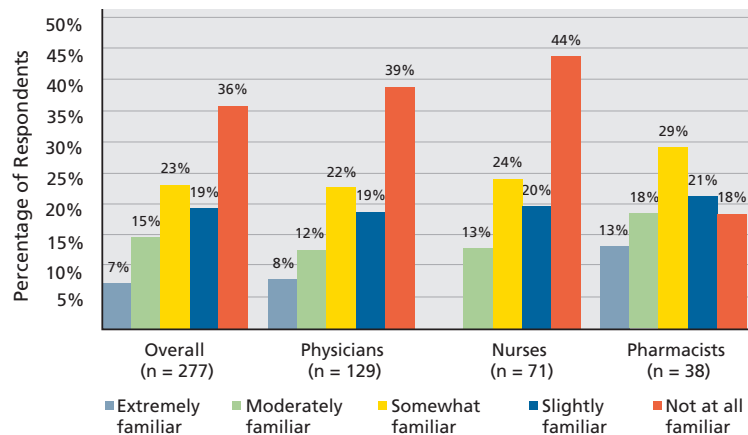
### Familiarity With Biosimilars Legislation

The first question in the survey asked respondents to rate their familiarity with recent biosimilar developments, including recent legislation providing an abbreviated approval pathway. As depicted in Figure 3, more than half of the respondents were either not at all familiar (36%) or slightly familiar (19%) with recent developments regarding biosimilars. A small percentage of respondents were extremely familiar with the recent developments (7%). When analyzing this question according to provider type, physician responses coincided with the overall results, whereas proportionally more nurses responded that they were not at all familiar with recent developments with biosimilars (44% of nurses). Only 18% of pharmacists responded that they were not at all familiar.

**Table 8** Distribution of Survey Respondents by Profession

Respondent	n	%
Physician	129	46.6%
Nurse	71	25.6%
Pharmacist	38	13.7%
Other clinician	7	2.5%
Other nonclinician	32	11.6%
Total	277	

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**Figure 3** Please rate your overall familiarity with developments for biosimilars, including recent legislation that provides an approval pathway for noninnovator (e.g., “generic”) manufacturers to introduce copies of biologics through an abbreviated review process.

### Interest in Prescribing, Dispensing, and Administering Biosimilars

The overall interest in prescribing, dispensing, or administering biosimilars appeared to be high, with 27% and 35% responding high and moderate interest, respectively (Figure 4). However, approximately one-fourth of respondents indicated that they require more information to make a decision regarding their future interest in using biosimilars. Again, physician responses coincided with the overall results, whereas approximately one-third of nurses indicated that they need more information. Incidentally, 39% of pharmacists indicated high interest in using biosimilars.

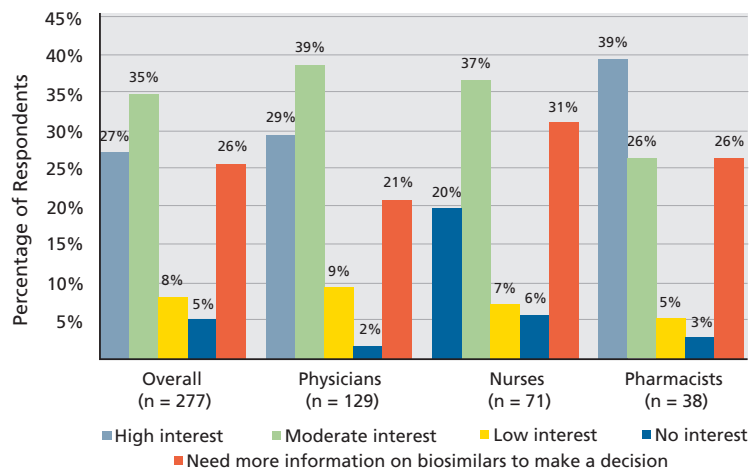
### Importance of Various Types of Information

To inform future educational efforts and to gauge what types of information clinicians will use when making

clinical decisions surrounding biosimilars, the survey asked participants to rate the importance of various types of information. The types of information inquired by the survey and the responses are depicted in Figure 5. Although overall results indicate that studies directly comparing the clinical end points (i.e., safety, efficacy) between a biosimilar and the reference product garnered the most responses for being “very important,” all of the types of information listed on the survey seem to be important, with at least 86% of respondents rating all types of information as somewhat or very important. Very few respondents listed any of these parameters as “not important.”

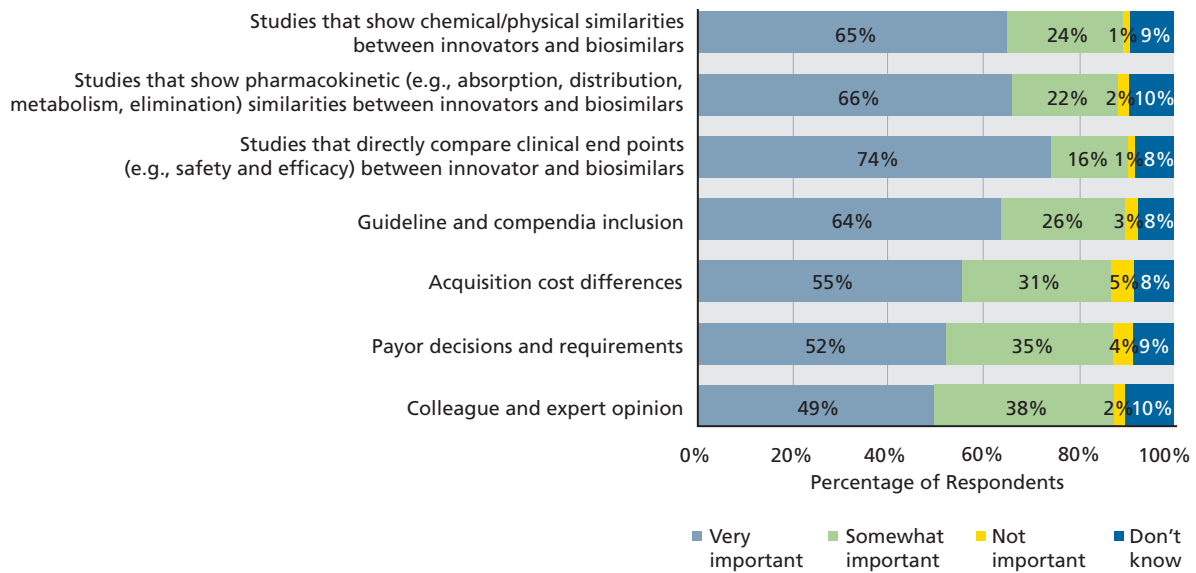
### Anticipated Use of Biosimilar Products

Lastly, the survey asked participants to consider a hypothetical situation in which biosimilars for specific



**Figure 4** Once approved by the FDA, what is your interest in prescribing, dispensing, or administering biosimilars in your practice setting?

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**Figure 5** As more information on biosimilars becomes available, how important are the following types of information in helping you decide to use biosimilar products?

biologic products are FDA-approved and available. The question asked how the respondent would proceed in using these different agents, such as whether they would: 1) immediately use them, 2) review and discuss them before using, or 3) would not consider using them. The reason to distinguish between different types of products is to assess whether differences in use would occur based on what type of biologic is being copied. As Figure 6 shows, no overall major differences existed between the different biosimilar products. A few respondents would immediately use each biosimilar agent, and even fewer would not at all consider using them, whereas most respondents would require review and discussion before using the biosimilar.

This question was also cross-referenced with familiarity with biosimilar developments (i.e., the first survey question). Those who are more familiar with biosimilar developments tended to have a more defined opinion regarding the immediate use of (or refusal to use) the biosimilar (Figure 7). Percentage-wise, fewer respondents indicated that they would require review and discussion for the extremely/moderately familiar group compared with the somewhat/slightly familiar group.

### Discussion and Survey Limitations

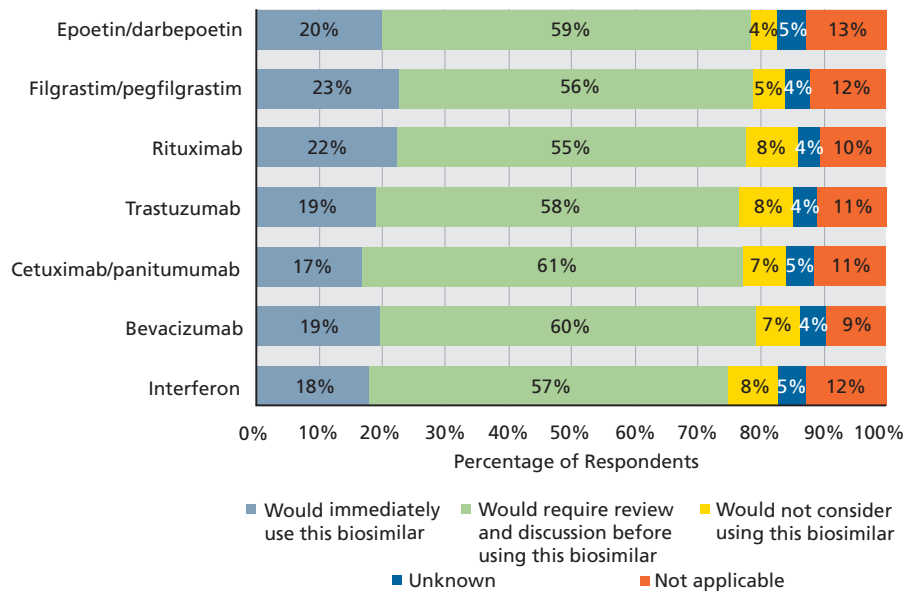
The data presented here represent a convenience sample of practicing clinicians, nonpracticing clinicians, and nonclinicians who attended the NCCN 16th Annual Conference. Therefore, the respondent pool

may not represent the general population of oncology practitioners in the United States. Furthermore, most respondents were not at all familiar or only slightly familiar with biosimilars legislation, and therefore the applicability of some of the more complex questions (e.g., regarding interest in using biosimilars and anticipated approach to using specific products) is uncertain.

Data from this survey indicated that more education regarding the principles surrounding biosimilars is necessary. The knowledge of recent biosimilar developments was suboptimal among respondents, and contributed to several indicating that they require more information before they can speculate on their interest in prescribing, dispensing, and administering biosimilars. Despite the relative unfamiliarity, much interest in using biosimilars was still seen.

Interestingly, the type of biosimilar did not seem to correlate with how clinicians plan to use the drug. The NCCN Work Group had hypothesized that the biosimilar agents for supportive care indications may be more readily used without review/discussion than those for the active treatment of cancer. Based on the survey, this appears not to be the case. Certainly, the suboptimal knowledge of biosimilar developments tended to influence the data, resulting in more respondents indicating that a review/discussion is required before readily using the product. Regardless, few clinicians seem to have come to a conclusion regarding the use of individual biosimilars. This high-

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**Figure 6** If a biosimilar was FDA-approved and available today for the following biologics, how would you proceed in routinely using the biosimilar instead of the innovator product tomorrow?

lights the need for access to emerging data showing comparability between the biosimilar and the reference product.

Despite the aforementioned limitations, the data provide insights as to some of the challenges regarding clinicians' knowledge about biosimilars. The need for additional education is probably because of the novelty of this concept in the United States. Currently no biosimilars are approved under the recent legislation establishing a biosimilar pathway, and the FDA has not yet issued any guidance document regarding its interpretation and implementation of the specific regulatory requirements or any other details of the pathway. Provider interest, and therefore the need for additional education, will likely increase when the first biosimilar is approved under this new abbreviated pathway. The work group discussed educational concepts and topics surrounding biosimilars that will help clinicians make the best decisions for their patients. Recommendations for education of clinicians and patients are provided.

### NCCN Biosimilars Work Group Recommendations/Consensus Statements and Discussion

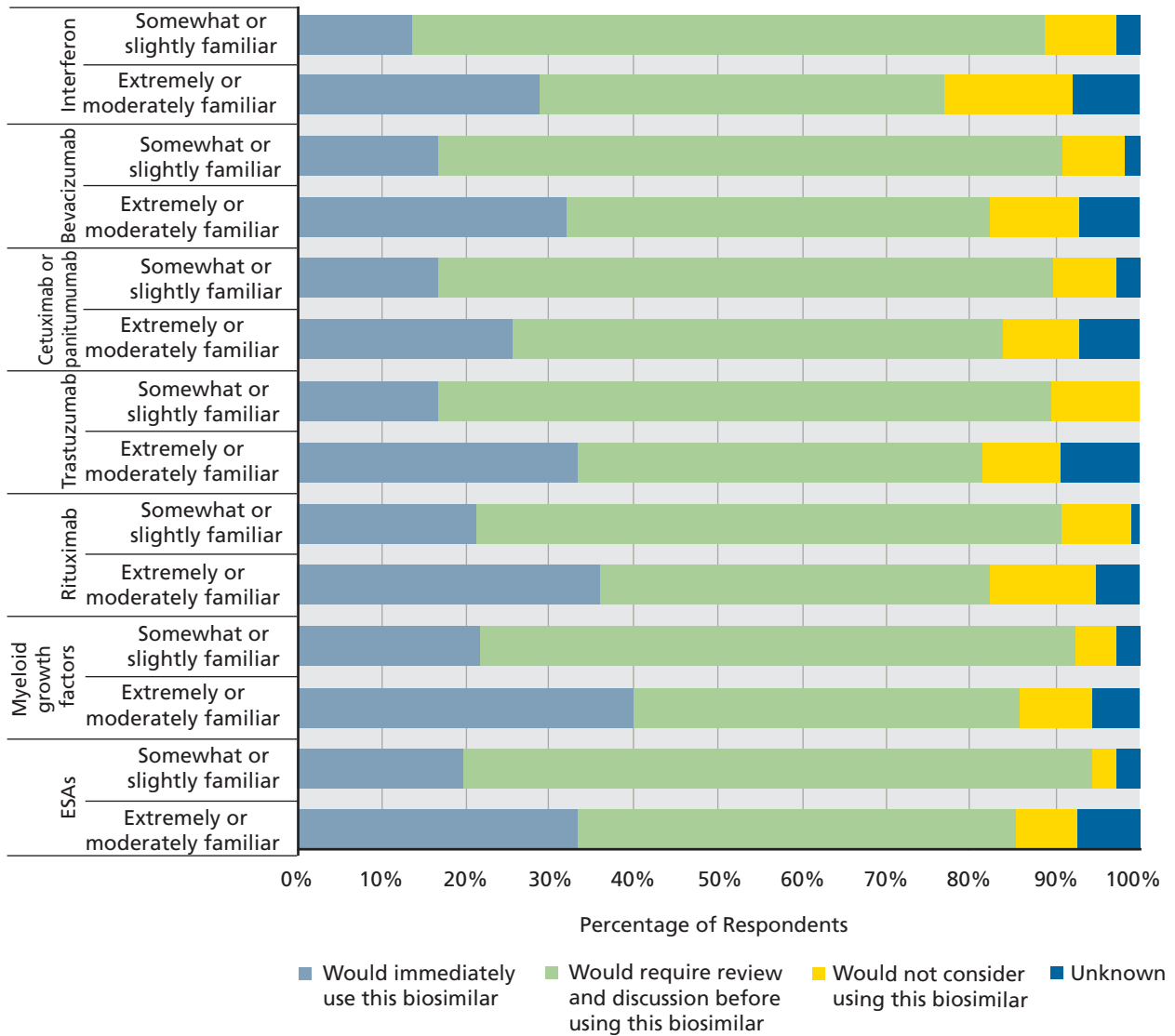
A list of the NCCN Work Group's consensus statements and recommendations for biosimilars in oncology practice are provided in Tables 2 and 3. The first

3 consensus statements in Table 2, referring to the importance of access and affordability, approval pathway, and standardization with reference product, are an affirmation by the work group of the importance of biosimilars in improving affordability and access to oncology medications. Furthermore, the work group supports the BPCI legislation and the approval pathway for biosimilars containing the elements mentioned in the table regarding the demonstration of similarity, the use of appropriate end points, and consistency/transparency of data, and of standardizing specific elements between the reference product and its biosimilar product.

Comments about legal and regulatory issues are limited because the goal of the work group was to concentrate on the patient care aspects of biosimilars in oncology. Patient care issues can be categorized into the following: tracking product use; addressing biosimilars in the NCCN Guidelines; using the P&T Committee; and the need for health care providers, policy makers, and patients to be educated about biosimilars.

Regarding the challenge of extrapolating the use of biosimilars to off-label indications, it was widely recognized that the appropriateness of extrapolation will depend on many variables. For example, a higher comfort level with extrapolating generally exists if factors such as the mechanism of action, use

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**Figure 7** Anticipated use of biosimilar products according to familiarity of recent biosimilar developments. Abbreviation: ESAs, erythropoiesis-stimulating agents.

with chemotherapy, and tumor type remain constant in the indication to which use is being extrapolated from how it was studied compared with the reference product. Ultimately, a determination of use in unapproved indications should and will be made by practitioners and patients on a case-by-case basis, based on the existing data package and perceived risks versus benefits. On the policy level, the NCCN Work Group recognized that mechanisms are already in place to make determinations about the appropriateness of extrapolation. First, because the recommendations in the NCCN Guidelines are well recognized by clinicians and payors, the work group recommended that individual NCCN Guideline

Panels should discuss the role of biosimilars in the context of their respective tumor type when appropriate. This should also include a recommendation for or against extrapolating to indications beyond the FDA-approved labeling.

Most biologics used in the active treatment of cancer are not routinely dispensed to the patient for self-administration; they are usually dispensed to health care providers for administration within an ambulatory clinic or inpatient setting. Thus, questions concerning substitution primarily lie with the biologics used for the supportive care management of cancer or chemotherapy symptoms that may be dispensed directly to patients for self-administration.

Secondly, institutional P&T Committees should actively evaluate biosimilar products to determine appropriateness in their specific patient population, including cost and safety considerations. This is in great contrast to hospital practices for generic small-molecule drugs, where typically generics are used immediately without oversight from P&T Committees, and subsequently hospitals realize immediate cost savings.

Furthermore, local institutional P&T Committees should also address issues regarding substitution practices through the formulary system. In community settings without P&T Committee review, the appropriate use of biosimilars should also be reviewed carefully. Biosimilar agents are expected to be formally discussed during routine committee meetings for subsequent development of policies governing their use, including whether the medical staff will allow for therapeutic interchange (whereby a P&T Committee can decide which molecules can be substituted) of these agents. Thus, few instances exist in which the inappropriate substitution by dispensers is of concern, and these situations fall primarily within the setting of community or specialty pharmacies.

In these situations, considering the use of biosimilars, confusion about automatic substitution arises when 1) the nonproprietary names are identical, and therefore the pharmacist cannot determine the prescribing physician's intended source (i.e., manufacturer) of the biologic, and/or 2) the payor will pay for the biologic from a different source other than what has been specified by the physician. In these cases, pharmacists should be aware of the laws governing substitution and whether the physician will need to be contacted regarding a change in product, thus highlighting the emphasis for provider education about these issues.

### **The Patient Perspective on Biosimilars in Oncology**

The NCCN Work Group included representation from the patient advocacy community, and issues about biosimilars from the patient perspective were discussed. The primary concern patients have about biosimilars is that they are safe, effective, and represent a quality treatment option compared with the innovator biologics. Patients do not want surprises and want regulatory issues to be clearly resolved to avoid potential safety risks. Patient and provider education about these products will help build trust in the science behind these drugs and a better understanding of how innovator biologics and biosimilars work and when substitution can occur.

The time required to conduct clinical studies that prove equivalent safety and efficacy of biosimilars or other drugs can often be lengthy, but these studies must be conducted in a manner that takes the minimum amount of time necessary to meet standards to ensure that patients with life-threatening diseases such as cancer have access to all available treatment options as quickly as possible. It is also important for patients to have access to cancer drugs, including biosimilars, where and when they are needed.

Patients also welcome the lower prices that are expected when biosimilars become available and provide more competition to existing biologics. The *Patient Data Analysis Report* recently released by the National Patient Advocate Foundation found that in 2009, 24% of the Patient Advocacy Foundation patients served reported “exceeded annual pharmacy benefit maximum” as the reason for needing assistance, and in 2010 this had increased to 27%. As many patients face challenges in paying for care, they have shown interest in understanding how payors will decide how and when to pay for biosimilars and how this will affect access to these drugs through pharmacy and potentially medical benefits.

Finally, it is important for patients to know that biosimilars are “highly similar” to their biologic reference products and “exhibit no clinically meaningful differences,” as stated in the BPCI Act, in addition to their having access to the data available for the products. This can be accomplished through increased educational efforts for patients, caregivers, clinicians, and other relevant stakeholders and through product labeling.

### **Closing Statement**

The NCCN Biosimilars Work Group is supportive of the recently passed legislation establishing a biosimilars approval pathway, and recognizes the important role that biosimilars can play in oncology care. The key goal of biosimilars is to increase the affordability and access to biologic medications for patients. The work group identified several challenges with integrating biosimilars into oncology practice, and discussions during the policy summit made it clear that clinicians, patients, and payors will look to NCCN for guidance about specific biosimilar products.

Moving forward, the oncology community awaits the release of the FDA's guidance to elucidate the existing biosimilars pathway, and this will likely answer



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some of the questions regarding expectations for regulatory approval of biosimilars. However, the guidance will not solve some of the challenges, such as how clinicians and payors will extrapolate the data to indications beyond the FDA-approved labeling. Although biosimilars may improve the access and affordability of expensive biologics in cancer care, it is not a panacea for the cost of care issues the country is currently facing, especially because the underlying cost savings and diffusion of biosimilars remains unknown.

As previously discussed, an NCCN Trends Survey suggests that provider knowledge of biosimilars is suboptimal. Fortunately, the widespread introduction of biosimilars into the United States market is expected to be a few years away, and therefore there is ample time for oncology providers, patients, and policy makers to become well informed about biosimilars and to keep abreast of any regulatory or legal policy changes or updates in this area.

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## NCCN Biosimilars White Paper

Individual Disclosures for the NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives					
Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
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