Biosimilars in Oncology: From Development to Clinical Practice

Katherine H. Rak Tkaczuk[a] *and Ira Allen Jacobs*[b]

Biologics play an integral role in the treatment of cancer not only for their therapeutic effects and ability to improve outcomes, but also as supportive care agents. Biologics are more complex to manufacture and take longer to bring to market. Because biologics are considerably more costly than small-molecule drugs, their use has placed an increasing economic demand on healthcare systems worldwide. Biosimilars are designed to be highly similar to existing branded biologics, but because biologics cannot be exactly copied, biosimilars should not be referred to as generic, exact versions of the innovator biologic. Biosimilars have the potential to increase access and provide lower cost options for cancer care as patent protection for some of the most widely used biologics begins to expire. Regulatory requirements for biosimilars are evolving, as are global harmonization and/or standardization strategies that can facilitate their robust clinical development. This review highlights critical factors involved with the integration of biosimilars into oncology treatment paradigms and practices. Clinicians will likely seek out practice guidelines and position statements from established scientific societies to help evaluate key information regarding biosimilars, such as efficacy, safety, comparability, and interchangeability with the reference biologic. Automatic substitution, nomenclature, extrapolation of clinical data from one indication to another, as well as parameters for ongoing pharmacovigilance are evolving considerations. Education of physicians and other healthcare providers, payers, and patients about biosimilars may facilitate informed decision making, promote acceptance of biosimilars into clinical practice, increase accessibility, and expedite associated health and economic benefits.
Semin Oncol 41:S3-S12

Biologics have become an important part of cancer treatment regimens.[1] As a result, major guidance documents in oncology now incorporate biologics into recommended treatment regimens. The addition of monoclonal antibodies such as bevacizumab and trastuzumab into the antineoplastic therapy armamentarium has helped to significantly improve key outcomes including progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone.[2] In contrast to cytotoxic chemotherapeutics, biologics have allowed cancer treatment to be more specific and targeted. Bevacizumab, for example, is designed to target vascular endothelial growth factor, whereas trastuzumab is designed to selectively inhibit the human epidermal growth factor 2 (HER2) receptor.[3,4] When used in combination with established chemotherapy regimens in patients with metastatic colorectal cancer, bevacizumab significantly improves OS, PFS, and overall response rate compared with chemotherapy alone.[3] Similarly trastuzumab used in combination with standard chemotherapy (doxorubicin + cyclophosphamide or paclitaxel) significantly improves key outcomes including time to progression, response rates, and 1-year survival in the subgroup of patients with HER2 overexpressed (+3 by immunohistochemistry) breast cancer.

[a]Professor of Medicine and Oncology, University of Maryland Cancer Center, Baltimore, MD.
[b]Pfizer Emerging Markets/Established Products Medicines Development Group, New York, NY.
This supplement was funded by Pfizer Inc.
Conflicts of interest: Katherine H. Rak Tkaczuk, MD, was a paid consultant to Pfizer Inc for the research and/or authorship of this supplement. Ira A. Jacobs, MD, MBA, FACS, is an employee of Pfizer Inc. Medical writing and editorial support to prepare this supplement was provided by Jennifer Ghith, MS, and Stephen Strudwick, PhD, of QD Healthcare Group and funded by Pfizer Inc.
Address correspondence to Katherine H. Rak Tkaczuk, MD, Professor of Medicine and Oncology, University of Maryland Cancer Center, 22 S Greene St, S9D12, Baltimore, MD 21201. E-mail: KTKACZUK@umm.edu
0093-7754

http://dx.doi.org/10.1053/j.seminoncol.2014.03.008

Table 1. Comparison of Biosimilars Versus Generic Small-Molecule Drugs[8,18]

	Biosimilars	Generic Drugs
Synthesis	Produced in living systems, generally using recombinant DNA technology	Produced through standard chemical synthesis
Identity with reference product	Designed and engineered to be similar, but cannot be 100% identical	Typically identical to the reference product
Structural features	Many layers of structure including primary, secondary, tertiary, quaternary, as well as post-translational modification	Typically simple molecular structure
Stability	Monitoring of manufacturing conditions required to maintain stability	Typically stable molecules
Immunogenicity	Immunologic testing and pharmacovigilance used to monitor for immunogenicity	Typically nonimmunogenic
Interchangeability	*Guidance pending* May or may not be interchangeable with the reference product – pending limitations on existing scientific methodologies	Interchangeable with the reference product, assuming similar purity and bioequivalence has been demonstrated
Automatic substitution	*Guidance pending* May or may not necessarily be automatically substituted with the reference product	Generally automatic substitution for the reference product is allowed
Nomenclature	International naming system for biosimilars is varied, US regulations for biosimilar naming are under development	Generally has the same INN as the reference product

Abbreviation: INN, International Nonproprietary Name.

Trastuzumab has provided the first truly targeted therapy for women with this type of cancer.[4] In the supportive care setting, erythropoietin and filgrastim are used to reduce the frequency of important cancer treatment–related events such as anemia and febrile neutropenia.[1,5–7]

Biologics are manufactured from living organisms and take longer to develop and bring to market relative to conventional therapies.[2] "Generic" versions of biologics cannot be manufactured due to the complexity of the proteins themselves (Table 1).[8] Biologics, including humanized monoclonal antibodies, are composed of large and structurally complex molecules. They require extensive immunogenic testing and pharmacovigilance strategies to monitor for the potential of evoking an immune (antibody) response (immunogenicity) (Table 1). Because biologic drugs cannot be exactly copied, the term "biosimilars" is used to describe biologics that are developed to be highly similar to existing, branded biologics.[9] The high level of similarity to the reference product is defined in terms of physicochemical characteristics, efficacy (including antitumor activity), and safety, based on the results of a comparability exercise that is outlined by regulatory authorities.[10,11] The benefits of biologics come at a cost. Often, they are more expensive than small-molecule therapies.[12] Some of the more widely used biologics in oncology are subject to patent expiration in the near future. Recently, the US Food and Drug Administration (FDA) provided initial draft guidance on a development and approval pathway for biosimilars in the United States, whereas regulatory guidelines have been developed and several biosimilars introduced in the European Union (EU) and elsewhere worldwide.[10,13] Clearly delineating biosimilars from the innovator product may help patients and physicians distinguish one product from another, and also maintain strict standards for ongoing pharmacovigilance reporting.[14]

In this review, the considerations associated with the integration of biosimilars into clinical practices in oncology, including the regulatory framework, need for global standards and harmonization, the role of clinical guidance documents, interchangeability and automatic substitution of biosimilars for existing branded biologics, safety monitoring, and questions relating to the overall acceptance of biosimilars by the oncology community are examined. All of these factors will need to come together for the successful integration of biosimilars into oncology practice (Figure 1).

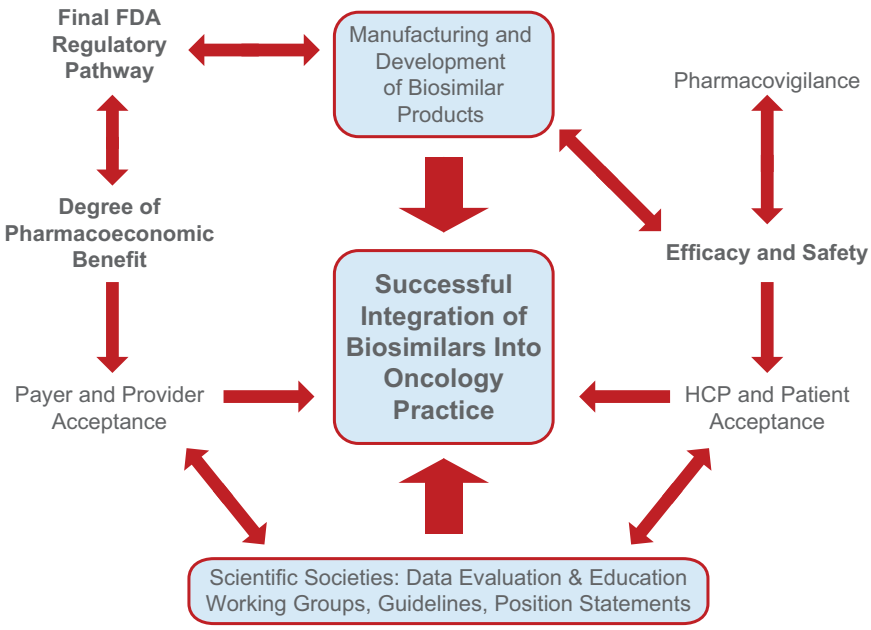

Figure 1. Parameters influencing the successful uptake and integration of biosimilars into US oncology practices. The US FDA will provide a finalized pathway for biosimilar approval; this pathway will, in turn, influence the manufacturing and development process and the amount of clinical data needed for approval. The efficacy and safety of biosimilars will be monitored via ongoing pharmacovigilance practices to ensure that potential immunogenicity or adverse events with a given biosimilar can be identified quickly and addressed. Scientific societies (eg, NCCN, ASCO) have a role in evaluating biosimilar data, educating HCPs and payers/providers, and providing consensus statements on the effective use of biosimilars. ASCO, American Society of Clinical Oncology; FDA, Food and Drug Administration; HCPs, healthcare providers; NCCN, National Comprehensive Cancer Network.

GUIDING PRINCIPLES FOR ESTABLISHING BIOSIMILARITY: THE EVOLVING REGULATORY FRAMEWORK

The European Medicines Agency (EMA) first established overarching guidance for development and approval of biosimilars, and the World Health Organization (WHO) has designed a regulatory framework that can be adapted to meet the needs of other countries. The general principles outlined in these guidance documents, as well as current draft FDA guidance, will likely influence the crafting of regulatory pathways for biosimilar development and approval in the United States and elsewhere in the world.[10,15,16] The Patient Protection and Affordable Care Act, signed into law by President Obama on March 23, 2010, amended the Public Health Service (PHS) Act to create a separate, abbreviated licensure process for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This process was created in a part of the law known as the *Biologics Price Competition and Innovation Act* (BPCI). Under the BPCI, a biological product may be demonstrated to be "biosimilar" if data demonstrate that the product is "highly similar" to an already-approved biological product.[17] The purpose of this act is to allow for licensure of biosimilars and interchangeable biological products that will be required to meet the exact FDA standards of safety and efficacy.

The overall goal of biosimilar development should therefore be not to replicate the existing efficacy and safety data package for a reference biologic, which would be an enormous waste of patient and public resources, but rather to demonstrate adequately sufficient similarity in chemical composition, biologic activity, and pharmacokinetics, so that existing efficacy and safety data for the reference biologic can be used.[8,18] The benefit of this approach is that it allows a more efficient development and approval process. In a recent survey of marketing applications and development programs for biosimilars, the EMA approved 14 applications for biosimilars, and four applications were rejected or withdrawn.[19] For the approved biosimilars, in the absence of corresponding differences in their biophysical properties from the reference biologic, none of the biosimilars were reported to have significant clinical variation from the innovator product.[19] The findings of this recent survey demonstrate the utility of the current EU biosimilar guidance and provide an example of how such regulatory processes have the potential to inform development of biosimilars in other countries.[19]

Although there is already an existing regulatory framework for biosimilar development, there will be

a need to closely monitor the evolution of manufacturing processes and standards. Under certain circumstances, the physicochemical characteristics of biologics can change over time (a characteristic termed "drift"), and because with biologics "the product is the [end result of the] process,"[18] even small changes in the manufacturing process for biologics have the potential to impact their efficacy, safety, and/or immunogenicity.[20,21] Owing to these characteristics of biologics, with manufacturing process changes, the manufacturer must demonstrate that the change in process does not produce clinically meaningful changes in efficacy or safety of the product.[21] The same general principles can be applied to demonstrating biosimilarity; these have been presented in guidance documents from the WHO as well as the EMA.[21] Revised guidance from the EMA was issued for public consultation in late 2013.[13]

CONSIDERING GLOBAL HARMONIZATION WITH BIOSIMILARS

As biosimilars are being developed and integrated into healthcare markets, global harmonization in standards for the development and approval of biosimilars is a key consideration.[21] This may lead to more timely development by manufacturers, followed by expedited approval, which may increase accessibility and affordability for patients. The guidelines from the WHO provide general principles and serve as a foundation for regulatory authorities in specific countries to develop their own approval pathways for biosimilars.[21] From this overarching guidance, individual guidelines for specific product classes also can be developed (eg, biosimilar erythropoietins, filgrastims) using experience gleaned from the reference product.[21,22] One notable example of the successful navigation of an approval pathway is the biosimilar infliximab, which is marketed separately by Celltrion (Remsima; Celltrion Healthcare, Incheon, South Korea), and Hospira (Inflectra; Hospira UK Limited, Warwickshire, UK). In late June 2013, the EU adopted a positive opinion for Remsima and Inflectra, making infliximab the first monoclonal antibody biosimilar approved in the EU.[23] The approval highlights the potential for experienced manufacturers to develop and market biosimilars, even for very large and structurally complex molecules, such as monoclonal antibodies.[24]

"Copy drugs" for several other biologics also have been introduced in emerging markets such as China, India, and Latin America. These drugs may not meet the definition of a biosimilar based on WHO, EMA, or FDA guidelines and therefore some may not consider them to be true biosimilars. India, for example, has demonstrated a robust acceptance and uptake of such 'copy' biologics.[25,26] Indeed there are more than 50 biopharmaceuticals approved for marketing in India, more than half of which are called 'similar' biologics.[27] In India, biosimilar development and use is driven to a large extent by the need for patient accessibility and affordability of life-saving medicines.[28] Overarching regulatory guidelines are evolving. The government of India, Department of Biotechnology and Central Drugs Standard Control Organization, published guidelines for biosimilars approval in 2012.[29] The guidelines provide information regarding requirements for preclinical evaluation of biological products that are 'similar' to approved reference products.[27] Such standards are different from those seen in EMA and FDA guidance for biosimilars.[10,11] With an increasing number of markets beginning to establish a regulatory framework for biosimilars, there will be pressure on emerging markets to define their own regulatory procedures in order to maintain global standards of quality and comparability in their biosimilars.[26] In 2010, Brazil developed a regulatory process for biosimilars with distinct pathways that are dependent on the degree of complexity of the biologic with corresponding levels of evidence required to prove sufficient efficacy and safety with the reference product. This system aims to help stimulate biosimilar development and innovation and increase utilization of biosimilars.[30]

CLINICAL PRACTICE GUIDELINES

Many guidance documents in oncology incorporate biologics for both therapeutic and supportive care purposes.[1] Guidance documents and position statements from established societies worldwide have the potential to help clinicians, payers, and providers understand key data relating to biosimilars and inform decisions regarding their use and place in the treatment paradigms (Figure 2).[31] Some societies expected to provide guidance on the use of biosimilars in oncology include the National Comprehensive Cancer Network (NCCN), American Society for Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO).

Since the introduction of biosimilars in Europe, position statements from European scientific societies have helped clinicians manage the unique set of considerations associated with using biosimilars such as erythropoiesis-stimulating agents (ESAs).[31,32] Clinical practice guidelines for the use of hematopoetic growth factors in the treatment of anemia and neutropenia in cancer patients have been issued by ESMO and are regularly updated.[7,33] A position statement from the European Renal Association – European Dialysis and Transplant Association

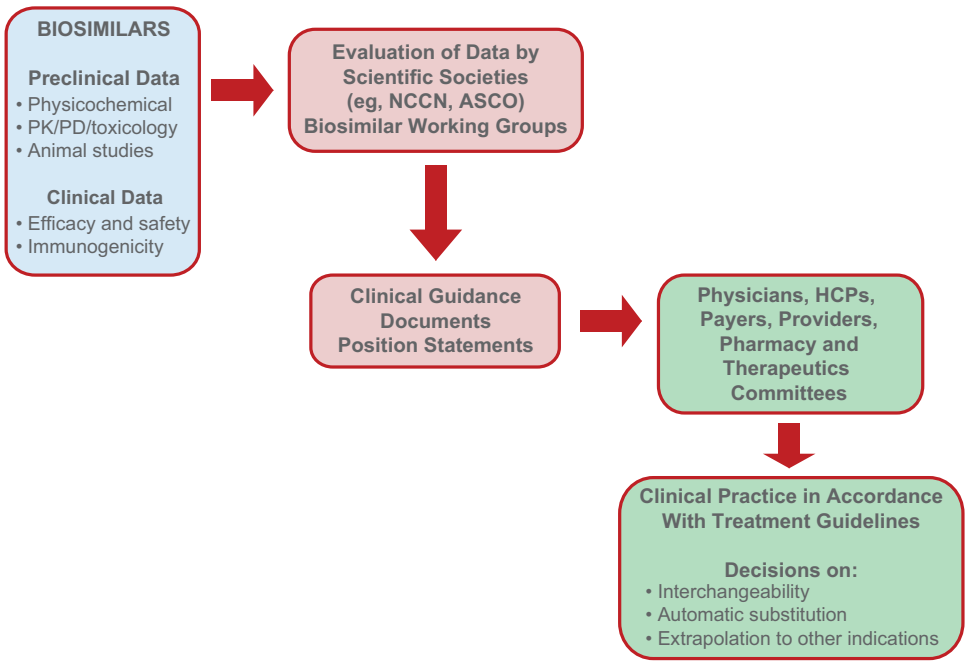

Figure 2. Potential role of scientific societies in evaluating biosimilar data. As in the European Union, scientific societies in the United States, such as the NCCN, will have an important role in evaluating preclinical and clinical data provided by manufacturers of biosimilars once they become available. Working groups then can provide clinical guidance and position statements. Physicians and other practitioners, payers, providers, and institutional committees will rely on such documents to set practice policy and make decisions on key issues pertaining to biosimilars, such as appropriateness of automatic substitution and extrapolation to other indications of the reference biologic. HCPs, healthcare providers; NCCN, National Comprehensive Cancer Network.

regarding ESAs recommends that the decision to use a biosimilar be based on a number of factors, including the prescribing physician's appropriate knowledge and understanding of the biosimilar in question, an adequate appraisal of the benefits and risks of using a biosimilar, and having a pharmacovigilance system in place to monitor for adverse events (AEs).[32] Another joint position statement from several Italian societies assessing the comparative data between biosimilars and their reference products stated that biosimilar erythropoietins showed comparable efficacy and safety with their reference biologic.[31] There were similar conclusions of therapeutic efficacy and safety in the case of at least three biosimilar filgrastims used for the treatment of chemotherapy-induced neutropenia.[31]

European Public Assessment Reports (EPARs) published by the EMA, have been helpful to clinicians to evaluate the appropriate use of biosimilars in Europe.[31] EPARs have been provided by the EMA upon recent approval of Remsima. Remsima was developed as a biosimilar product to Remicade (infliximab; Janssen Biotech, Inc., Horsham, PA), was approved for similar indications as Remicade, and has a stringent pharmacovigilance program in place for ongoing assessment that is detailed specifically within the EPAR.[34,35] As biosimilars in oncology begin to be approved for use in the United States, guidance from NCCN panels will be needed to advise Pharmacy and Therapeutics Committees and individual practitioners on the use of biosimilars for a specific tumor type or indication (see Figure 2). Since 2011, the NCCN has held invitation-only biosimilar policy summit meetings, and a white paper of the NCCN Biosimilars Work Group recommendations was published in 2011.[1]

INTERCHANGEABILITY AND AUTOMATIC SUBSTITUTION

Interchangeability refers to the ability of two products to be exchanged with each other without a significant risk of an adverse health outcome.[20] In the US Biologics Price Competition and Innovation Act of 2009 (a component of the Affordable Care Act), interchangeability is defined as a higher standard than biosimilarity because it allows the product to be substituted for the reference product without the healthcare provider's intervention.[1,36] In its draft guidance, the FDA has further suggested the definition of this higher standard of interchangeability (based on the statutory language) be that the biosimilar product can be expected to produce the same effect as the reference biologic product "….*in*

Table 2. Draft US FDA Guidance: Criteria for Interchangeability of Biosimilars[36]

- Sufficient information has been provided to demonstrate biosimilarity[a] of the product with the reference biologic
- The biologic product is *"expected to produce the same clinical result as the reference product in any given patient"*; AND
- *"If the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch"*

[a] The FDA defines biosimilarity as: *"the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"* and *"there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."*[36]

any given patient"; the standard of interchangeability as defined also assumes there is no greater efficacy or safety risk observed when switching between the products (Table 2).[15,36] Interchangeability therefore requires an expectation that the safety and efficacy risk is not greater than the reference product not only in the population but at the individual patient level, and this is, necessarily, a very high standard that may be difficult to establish on a scientific basis.[12,20] Although guidance from the EMA sets the criteria for biosimilarity in the EU, the individual countries within the EU may have their own policies regarding the interchangeability of biosimilars and their reference products.[37]

Automatic substitution is the practice whereby substitution of a branded product occurs at the dispensing level when a pharmacist elects to change a product without the prescribing physician's prior consent. Existing policies regarding automatic drug substitution for generics as well as biosimilars in the United States are governed by state laws, which can vary according to the state in question.[1,38] Generally, in the case of small-molecule generic drugs, all that needs to be proven for automatic substitution is biochemical identity with the reference product and demonstrated bioequivalence.[8] Because biosimilars are not generics, it cannot be assumed they can be automatically substituted for branded biologics without the prescribing physician's consent. In this regard, whereas the EMA has the authority to determine that a product is biosimilar to its reference biologic, it does not have the authority to state whether it can be automatically substituted for a branded innovator biologic; as with interchangeability, this is left for the individual European countries within the EU to determine.[8] It has been advised by some societies (such as ESMO) in Europe that the right to prohibit automatic substitution be retained for specific patients as determined by the prescribing physician's discretion.[31] The rationale behind these policies is, in part, to avoid changes in therapy for treatment-experienced patients who have tolerated a given biologic.[31,38] However, once available, clinicians may be more inclined to initiate therapy with a biosimilar as opposed to a potentially higher priced reference biologic in treatment-naïve patients.[20,31] It should be noted that existing drug substitution policies were designed for generic small-molecule drugs and do not necessarily apply to biosimilars. Recently, California Governor Jerry Brown vetoed legislation designed to allow substitution of biosimilars designated as interchangeable by the FDA. This legislation would have required notification of both prescribing physician and patient of the substitution.[39,40] Debate in this area is likely to continue in several other states, with Massachusetts and Pennsylvania considering similar measures.[39] Furthermore, it is likely that institutional Pharmacy and Therapeutics Committees in the United States may conduct their own analyses based on safety and efficacy data, as well as cost considerations, and come up with their own local guidelines, although these committees often follow the FDA approval guidelines for the particular agent.[1,14] As more biosimilars enter the market and clinical experience with these products increases, policies surrounding interchangeability and automatic substitution of specific types of biosimilars will continue to evolve.

POSTAPPROVAL: SAFETY CONSIDERATIONS

Pharmacovigilance

As is the case with most biologics, including biosimilars, clinical testing preapproval may not identify all possible AEs; an evaluation of clinical safety therefore is continued in the postmarketing setting.[13,16] WHO guidance provides recommendations for post-marketing safety reports for product tolerability, and such reports include a scientific evaluation of frequency/causality of AEs.[16] The WHO also recommends that, following approval, the manufacturer have a system in place to detect and assess, understand, and prevent any potentially drug-related AEs. This system, referred to as pharmacovigilance, also provides for notification regarding the occurrence of such AEs in whatever countries the product may be marketed.[16]

As with any drug, the goal of a postapproval pharmacovigilance plan is to identify and understand, as fully as possible, the frequency and nature of AEs associated with a specific product, including potential risk factors for such AEs.[41] To address safety considerations, the EMA mandates postapproval monitoring, as well as pharmacovigilance plans for biologic drugs, including biosimilars.[20] In addition, the WHO and EMA recommend that if, based on clinical experience, any additional specific safety monitoring or pharmacovigilance plan has been required for the reference biologic, or its specific product class (eg, ESAs), the same plan should be applied to the biosimilar.[13,16] Likewise, if additional concerns (eg, increased immunogenicity of the biosimilar) have arisen during the evaluation of the biosimilar product, these also may be evaluated through appropriate safety monitoring.[13,16]

The FDA position and requirement for pharmacovigilance has not been specifically defined for biosimilars but existing FDA guidance on Good Pharmacovigilance Practice considers routine spontaneous AE reporting to be sufficient postmarketing surveillance for products where no safety risks have been identified pre- or post-approval, and if used in adequately studied populations.[41] The FDA considers a specific pharmacovigilance plan as appropriate, however, in the event the at-risk population needs additional study, or if safety risks have been identified either pre- or post-approval.[41] As defined by existing FDA guidance, such a pharmacovigilance plan could include additional measures beyond routine reporting, such as expedited reporting of serious AEs, active surveillance for specific AEs, creation of product registries, pharmacoepidemiologic studies, or additional clinical trials.[41] Experience to date with biosimilars outside the US is limited; however, label changes have not been required due to safety concerns with a specific product.[42] Despite this, there are still strong pharmacovigilance programs in place.[42] The recent EMA approval of the biosimilar Remsima included a stringent pharmacovigilance program for ongoing product assessment.[34]

Nomenclature and Product Labeling Considerations

Naming is an important consideration when developing regulatory policies for biosimilars because of its potential impact on physician prescribing or patient bias, interchangeability, as well as pharmacovigilance.[1,14] Regulatory agencies are in the process of developing standards for biosimilar nomenclature.[1] It is important that biosimilars have names that make them readily distinguishable from the innovator biologic (as well as other biosimilar products).[1,14] This is necessary to make certain that adverse events that occur in the post-market setting can be readily and correctly matched to a specific product.[1,9] Using the example of erythropoietin-based products, the current WHO system assigns the group name *-poetin* as well as a random prefix to indicate changes in the amino acid chain (eg, *darbopoetin*) and a Greek letter to indicate differences in glycosylation (eg, *epoetin alpha*).[22] This system has resulted in at least 10 different nonproprietary names for the available erythropoietins.[22] Some position statements suggest the International Nonproprietary Name (INN) system should not be used to prescribe biologic drugs.[31] One of the reasons for this is that INN nomenclature with biosimilars can lead to problems, for example, if some countries allow pharmacists to auto-substitute a less expensive drug having the same INN as its reference product.[32] Instead, naming according to product brand has been recommended to enable better pharmacovigilance of biosimilars, so specific events can be associated with the correct product and manufacturer.[9,31]

EXTRAPOLATION OF DATA

The draft FDA and the current WHO guidance allow the use of clinical efficacy and safety data for one indication to be extrapolated to other indications for the reference biologic.[10,16] In general, guidelines suggest that extrapolation of data may be allowed for biosimilars as long as sufficient justification can be provided for the new indication (eg, similar anticipated mechanism of action for the biosimilar) and a rationale for similar pharmacokinetics, efficacy, safety, and immunogenicity can be provided for the new indication target population (Table 3).[10] This is similar to the existing WHO guidance on extrapolation of clinical data.[16]

Examples from the European experience have shown that data for one indication of an innovator may be reasonably extrapolated to another. The approval of biosimilar erythropoietins for anemia in cancer is based largely on extrapolation of data for other approved indications (eg, use in chronic kidney disease), and guidelines have thus far allowed this.[31] This has been allowed on the basis of similar mechanism of action between indications due to the fact there is only one identified erythropoietin receptor and a common route of administration; for indications where this does not apply, additional clinical data may be required.[31] Results for the use of biosimilar filgrastims for chemotherapy-induced neutropenia also have allowed extrapolation to other clinical indications of the innovator product, including transplantation, and peripheral blood progenitor cell mobilization without direct clinical equivalence data.[31] Remsima was designed to replicate the reference product

Table 3. Draft US FDA Guidance: Criteria to Consider When Extrapolating Clinical Data for Biosimilars to Other Indications of the Reference Product[10]

- Does the product first meet criteria for biosimilarity with the reference product as evidenced by clinical study to demonstrate purity, safety, and potency in one condition of use for the reference product?
- Is a similar mechanism of action expected for the proposed indication (eg, target receptor, binding and dose response, relationship between product structure and target/receptor interactions, signaling pathway, location and expression of target receptor)?
- Can similar pharmacokinetics be expected in the patient population?
- Is there any anticipated difference in toxicity in the desired patient population?
- Are there other factors that may influence safety and efficacy in the target population for the new indication (eg, comorbidities, concomitant medications)?

Remicade (infliximab) in terms of pharmaceutical composition, dosage strength, and route of administration, and data were extrapolated to other indications of the reference product.[34,35]

ACCEPTANCE OF BIOSIMILARS BY THE COMMUNITY

Physicians and other healthcare providers and patients will play a key role in determining how biosimilars are integrated into clinical practice.[1,14] In a recent survey of Italian oncologists regarding the use of ESAs for chemotherapy-induced anemia, almost half (45%) anticipated using biosimilars in place of the originator product, with 54% of these respondents noting lower price as the motivation for use, and 26% regarding their use as scientifically supported.[43] Notably, among the 55% who did not feel biosimilars were an adequate replacement for the branded product, 42% cited a lack of studies to support their use.[43] Biosimilars have not yet entered the US market and the regulatory pathways are under development, but there is a desire for information regarding their use, including efficacy and/or safety data, as well as immunogenicity data.[32] Experience in Europe has shown biosimilars can be developed that have acceptable efficacy and safety profiles.[9,44] Use of biosimilar filgrastims in the EU has shown that they have met regulatory requirements adequately and compare favorably in terms of efficacy and safety with the reference biologic.[9]

The results from an NCCN survey conducted with a US audience in 2011 suggest that overall interest in using biosimilars, once approved by the FDA, was moderate (35%) or high (27%) among the study group, which consisted of physicians, nurses, and pharmacists.[1] Similar to questions regarding small-molecule generic drugs, some of the main questions for prescribing physicians and other practitioners that will influence their attitudes regarding biosimilars will likely be[8,45]:

- Do biosimilars have highly similar activity compared with the reference biologic?
- Do these drugs have a highly similar efficacy and safety profile compared with the reference biologic?
- How interchangeable are biosimilars with the reference product?
- Can data for one indication of the reference product be extrapolated to another indication for which no formal studies have been conducted?
- Will the availability of lower cost biosimilars allow healthcare practitioners to adhere to established international guidelines?

The scientific principles guiding biosimilar development are similar to those used following a manufacturing process change. State-of-the-art analytical techniques can detect minute difference between products and are being used to verify that biosimilars are highly similar to the reference product in terms of structural and functional performance as well as clinical activity.[8] The evolving regulatory processes that have been successfully implemented in Europe and elsewhere will help clarify considerations currently under debate such as interchangeability and extrapolation of data.

Central to the issue of acceptance is the education of physicians, other healthcare practitioners, patients, and payers on biosimilars and the regulatory issues surrounding them.[1,2,14] Data from the 2011 NCCN survey suggest there may be limitations in overall knowledge of biosimilars in the medical community.[1] About a quarter of the respondents to the survey reported needing additional information on biosimilars in order to make their decisions about future use.[1] Some oncologists may be reluctant to prescribe a biosimilar for the treatment of cancer in the absence of knowledge regarding a clinical data package supporting its use in the particular indication.[1,14] With the introduction of biosimilars, patients might be more likely to opt for the potentially lower priced biosimilar, particularly if they are incurring significant out of pocket costs.

As a result, payers potentially may benefit in terms of budget impact.[20] The present environment of increasing healthcare costs and the growing role of patients in treatment decisions have the potential to be contributing factors driving the uptake of biosimilars.

SUMMARY AND CONCLUSIONS

Biosimilars have the potential to increase access to therapies and may offer benefit to healthcare systems dealing with the increasing costs of cancer care.[2,44] In the current environment there is evidence that oncologists are increasingly considering cost-effectiveness as part of their treatment decisions. In a study of 118 community-based oncologists, nearly 60% reported they now consider drug costs in clinical decision making, roughly half reported the need to change treatment plans due to the loss of medical insurance, and 58% reported that patients refused treatment due to financial concerns (including out-of-pocket costs).[46] The successful integration and uptake of biosimilars in oncology may help to expand choices for clinicians and patients and increase accessibility to potentially beneficial treatments.

Biosimilar manufacturers and the healthcare community are awaiting final guidance from the FDA for biosimilar approval.[12] Global standards, at least regarding the fundamental aspects of biosimilar development, have the potential to benefit the community as a whole by encouraging manufacturing and innovation of biosimilar products that can then be effectively marketed on a global scale. Figure 1 illustrates the interrelationship among the FDA regulatory approval pathway, manufacturers of biosimilar products, scientific societies, and the overall acceptance and uptake of biosimilars into clinical practice.[1,12,31] Input and consensus from all stakeholders ultimately will help to shape the evolving regulatory and approval process for biosimilars. Biosimilars continue to represent an opportunity to increase access and reduce costs for patients and healthcare systems.

REFERENCES

1. Zelenetz AD, Ahmed I, Braud EL, et al. NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. J Natl Compr Canc Netw. 2011;9 (Suppl 4):S1–22.
2. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. Targ Oncol. 2012;7(Suppl 1): S57–67.
3. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.
4. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
5. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47:8–32.
6. Silvestris N, Del Re M, Azzariti A, et al. Optimized granulocyte colony-stimulating factor prophylaxis in adult cancer patients: from biological principles to clinical guidelines. Expert Opin Ther Targets. 2012;16 (Suppl 2):S111–7.
7. Schrijvers D, De Samblanx H, Roila F. ESMO Guidelines Working Group. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. Ann Oncol. 2010;21(Suppl 5):v244–7.
8. Weise M, Bielsky M-C, De Smet K, et al. Biosimilars: what clinicians should know. Blood. 2012;120:5111–7.
9. Gascón P, Tesch H, Verpoort K, et al. Clinical experience with Zarzio in Europe: what have we learned? Support Care Cancer. 2013;21:2925–32.
10. United States Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed May 15, 2013.
11. European Medicines Agency. Guideline on similar biological medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf. Published April 26, 2013. Accessed October 10, 2013.
12. Ventola CL. Biosimilars: part 1: proposed regulatory criteria for FDA approval. P&T. 2013;38:270–87.
13. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf. Accessed October 24, 2013.
14. DeMartino JK. Biosimilars: approval and acceptance? J Natl Compr Canc Netw. 2011;9(Suppl 3):S6–9.
15. Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. N Engl J Med. 2011;365:385–8.
16. World Health Organization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed October 10, 2013.
17. United States Food and Drug Administration. How drugs are developed and approved. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/. Accessed October 29, 2013.
18. Jeske W, Walenga JM, Hoppensteadt D, Fareed J. Update on the safety and bioequivalence of

biosimilars—focus on enoxaparin. Drug Healthc Patient Saf. 2013;5:133–41.
19. Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther. 2012;34:400–19.
20. Blackstone EA, Fuhr JP, Jr. Innovation and competition: will biosimilars succeed? Biotechnol Healthc. 2012;9:24–7.
21. Schiestl M. A biosimilar industry view on the implementation of the WHO guidelines on evaluating similar biotherapeutic products. Biologicals. 2011;39:297–9.
22. Minghetti P, Rocco P, Del Vecchio L, Locatelli F. Biosimilars and regulatory authorities. Nephron Clin Pract. 2011;117:c1–7.
23. European Medicines Agency. Summary of opinion (initial authorization): Remsima (infliximab). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_Initial_authorisation/human/002576/WC500144832.pdf. Accessed September 23, 2013.
24. Biotech Primer. First biosimilar monoclonal antibody approved. http://biotechprimer.com/biotech-primer-blog/89-first-biosimilar-monoclonal-antibody-approved Accessed October 24, 2013.
25. Misra M. Biosimilars: current perspectives and future implications. Indian J Pharmacol. 2012;44:12–4. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271516/?report=printable. Accessed October 9, 2013.
26. Mody R, Goradia V, Gupta D. How similar are biosimilars in India? A blind comparative study. Pharma Focus Asia. 2010;11:1–8. http://www.pharmafocusasia.com/research_development/blind-comparative-study.html. Accessed October 9, 2013.
27. Generics and Biosimilars Initiative Online. India releases draft 'similar biologic' guidelines. http://www.gabionline.net/Guidelines/India-releases-draft-similar-biologic-guidelines. Accessed October 11, 2013.
28. Nellore R. Regulatory considerations for biosimilars. Perspect Clin Res. 2010;1:11–4.
29. Guidelines on Similar Biologics: regulatory requirements for marketing authorization in India. Government of India. Department of Biotechnology, Central Drugs Standard Control Organization. 2012. http://dbtbiosafety.nic.in/Files%5CCDSCO-DBTSimilarBiologicsfinal.pdf. Accessed October 11, 2013.
30. Azevedo VF, Sandorff E, Siemak B, Halbert RJ. Potential regulatory and commercial environment for biosimilars in Latin America. Value Health Regional Issues. 2012;1:228–34.
31. Barosi G, Bosi A, Abbracchio MP, et al. Key concepts and critical issues on epoetin and filgrastim biosimilars. A position paper from the Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation. Haematologica. 2011;96:937–42.
32. Covic A, Cannata-Andia J, Cancarini G, et al. Biosimilars and biopharmaceuticals: what the nephrologists need to know—a position paper by the ERA-EDTA Council. Nephrol Dial Transplant. 2008;23:3731–7.
33. Crawford J, Caserta C, Roila F. ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. Ann Oncol. 2010;21(Suppl 5):v248–51.
34. European Medicines Agency. Assessment report: Remsima (infliximab). 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/002576/WC500151486.pdf. Accessed October 29, 2013.
35. Remicade (infliximab) Prescribing Information, Janssen Biotech, Inc., Horsham, PA. March 2013.
36. United States Food and Drug Administration. Guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformatin/Guidances/UCM291134.pdf. Accessed May 15, 2013.
37. Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. Eur J Haematol. 2011;86:277–88.
38. Kanter J, Feldman R. Understanding and incentivizing biosimilars. Hastings Law J. 2012;64:57–83.
39. Pollack A. New York Times. Governor Brown of California Vetoes Biotech Drug Bill. Available at: http://www.nytimes.com/2013/10/14/us/gov-brown-of-california-vetoes-biotech-drug-bill.html?r=0&pagewanted=print. Accessed October 24, 2013.
40. State of California Senate Bill No. 598. September 4, 2013.
41. United States Food and Drug Administration. Guidance for industry: good pharmacovigilance practices and pharmacoepidemiologic assessment. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf. Accessed October 10, 2013.
42. Ebbers HC, Crow SA, Vulto AG, Schellekens H. Interchangeability, immunogenicity and biosimilars. Nat Biotechnol. 2012;30:1186–90.
43. Cortinovis D, Beretta G, Piazza E, et al. AIOM Lombardia. Chemotherapy-induced anemia and oncologist perception on treatment: results of a web-based survey. Tumori. 2013;99:45–50.
44. Vulto AG, Crow SA. Risk management of biosimilars in oncology: each medicine is a work in progress. Targ Oncol. 2012;7(Suppl 1):S43–9.
45. Aapro MS. What do prescribers think of biosimilars? Targ Oncol. 2012;7(Suppl 1):S51–5.
46. Cote B. Oncologists: cost-effectiveness policy necessary despite quality of care warnings. Oncology Business Review. 2009. http://www.oncbiz.com/documents/OBR_SEPT_MRR.pdf. Accessed October 11, 2013.