VOLUME 36 · NUMBER 12 · APRIL 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Statement: Biosimilars in Oncology

Gary H. Lyman, Edward Balaban, Michael Diaz, Andrea Ferris, Anne Tsao, Emile Voest, Robin Zon, Michael Francisco, Sybil Green, Shimere Sherwood, R. Donald Harvey, and Richard L. Schilsky

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on February 14, 2018.

R.D.H. and R.L.S. contributed equally as co-senior authors.

Corresponding author: Gary H. Lyman, MD, MPH, Hutchinson Institute for Cancer Outcomes Research Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, MS-B232, Seattle, WA 98109-1024; e-mail: glyman@fredhutch.org.

0732-183X/18/3612w-1260w/$20.00

ABSTRACT

As many biosimilars come to market in the next several years, their use in oncology will play an important role in the future care of patients with cancer. ASCO is committed to providing education and guidance to the oncology community on the use of biosimilars in the cancer setting; therefore, ASCO has developed this statement to offer guidance in the following areas: (1) naming, labeling, and other regulatory considerations, (2) safety and efficacy of biosimilars, (3) interchangeability, switching, and substitution, (4) value of biosimilars, and (5) prescriber and patient education.

J Clin Oncol 36:1260-1265. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Despite considerable advances in cancer care, rising health care costs have prompted the need for cost-containment strategies.[1] This is especially true with regard to new oncology pharmaceuticals—eight of the 10 most expensive drugs on the market are cancer drugs. Since the enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010, biosimilars have been developed and marketed as competitive, lower-cost alternatives to newer biologic treatments. In 2013, the Virginia Generally Assembly defined a biological product as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein other than a chemically synthesized polypeptide, or analogous product, or arsphenamine or any derivative of arsphenamine or any other trivalent organic arsenic compound, applicable to the prevention, treatment, or cure of a disease or condition of human beings. Biosimilar was defined as a biologic product that is highly similar to a specific reference biologic product, notwithstanding minor differences in clinically inactive compounds, such that there are no clinically meaningful differences between the reference biologic product and the biologic product that has been licensed as a biosimilar pursuant to 42 USC section 262(k) in terms of safety, purity, and potency of the product.

To date, the US Food and Drug Administration (FDA) has approved eight biosimilar products for use in the United States, including one product for use as a supportive care agent in the cancer setting (filgrastim-sndz, for use as an alternative to filgrastim) and two products for use in the treatment of cancer (bevacizumab-awwb, for use as an alternative to bevacizumab, and trastuzumab-dkst, for use as an alternative to trastuzumab). With the expiration of several biologic patents, a wave of biosimilars is expected in the United States, and cancer treatments are likely to consist of a significant proportion of the approved biosimilars. In fact, oncology biologic products with patents scheduled to expire by 2020 total global annual spending of more than $20 billion. The biosimilars for these products are expected to take over the majority of this market share.[2]

Whereas access to biosimilars could potentially reduce the cost of cancer therapies, inconsistent use and a lack of understanding of the terminology, evolving regulatory guidance, and questions about how biosimilars may be prescribed and dispensed, have contributed to an uncertain environment for all stakeholders. Moreover, there is growing concern that existing statutes regarding the regulation of generic drugs may be misapplied to biologic products, which has led several states to amend older state laws to address the complex molecular characteristics of biologics and biosimilars. ASCO, along with many other organizations, has commented on the evolving regulatory framework for biosimilars.[3,4] In addition, it has been noted in prior publications that physicians were initially concerned about the use of generic drugs and even the first monoclonal antibody therapies[5]; therefore, ASCO

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.77.4893

DOI: https://doi.org/10.1200/JCO.2017.77.4893

has developed this statement to provide education and guidance to the oncology community on the assessment of the safety and efficacy of biosimilars in the cancer setting. In doing so, ASCO offers guidance on the following issues:

- Safety and efficacy of biosimilars: Clinical standards and postmarket evidence development are essential components of the ongoing development of new products to ensure the safe and effective delivery of care. Oncologists play a critical role in the gathering and reporting of robust postmarket evidence. Sustained postmarket evidence development is necessary to enhance patient and provider confidence in biosimilars and to supplement the evidence supporting the safe and effective use of biosimilar products.
- Interchangeability, switching, and substitution: The ability of oncologists and patients to decide which biologic product will provide optimal treatment is key to providing high-quality, high-value cancer care. The interchangeability of a product is determined at the federal level after FDA review; however, substitution will be regulated at the state level. As individual states work to regulate the use of biosimilars, in accordance with the FDA designation, oncologists and patients must be aware of the regulations, authorities, and responsibilities that may affect their treatment choices.
- Naming, labeling, and other regulatory considerations: To effectively choose, prescribe, or administer biosimilars, it is important that providers understand the comparative risks and benefits of biologic products. Biosimilarity refers to similarity to a reference product, and does not imply similarity to other biosimilars. With biosimilars, the name alone may not be enough to help providers differentiate between products. The naming and labeling of biosimilars, considered together, will help to ensure that oncologists, pharmacists, and other providers have all the necessary information to ensure they are using their chosen therapy as intended.
- Value of biosimilars: Oncologists recognize the effect of cost and reimbursement in making treatment decisions. Biosimilars provide an opportunity to both obtain desired outcomes and manage the cost of care for patients with cancer. Coverage and reimbursement policies vary by payer, patient, and setting. In addition, use management policies are often used as a way to manage cost, without necessarily considering clinical information.
- Prescriber and patient education: Continuous provider education is critical to inform, promote, and use biosimilar products in a medically appropriate and cost-effective way to treat cancer. Also important is patient education about biosimilars provided by a knowledgeable health care professional. Public awareness and education, and the use of standardized, publicly available materials from professional societies, government sources, and patient advocacy groups will help to ensure understanding of biosimilars.

SAFETY AND EFFICACY OF BIOSIMILARS: CLINICAL STANDARDS AND POSTMARKET EVIDENCE DEVELOPMENT

Confidence in the safety and efficacy of biosimilars is of the utmost importance in clinical practice. The FDA approval process for biosimilars makes it less likely that large, phase III trials will be undertaken for all approved indications of the reference product. In fact, if the same level of evidence was required for biosimilars as that for original biologics, the potential for cost reduction would not likely be realized; therefore, approval of the biosimilar for other indications must largely be based on extrapolation, and the appropriate incorporation of biosimilars into practice is left largely to clinical experience and judgement. Product drift—product changes that can occur over time as a result of manufacturing changes, processing, and packaging—may result in differences in both biosimilars and the originator biologic over time. Currently, when there are postapproval changes to either the reference product or the biosimilar, the FDA requires data to demonstrate that any postapproval changes to the product do not result in clinically meaningful changes in safety or efficacy.

Given that regulatory review of biosimilars, compared with reference products, relies less on clinical data and more on structural, functional, and pharmacologic data, there will be a greater reliance on postmarket evidence development to demonstrate the value of these products to stakeholders. Indeed, postmarket research will provide additional data on the risks and benefits of switching biologic therapies.

Clinicians play an essential role in postmarket surveillance efforts. Postmarket surveillance is necessary to generate data on use, efficacy, and safety, which may not have been apparent during premarket trials and informs the optimal use of the drug in diverse populations. This process educates patients, clinicians, and regulators, and, importantly, may result in changes to product labels, compendia, or clinical pathways and practice guidelines.

However, the United States has and will continue to have significant challenges with collecting these data, given the fragmented nature of the US health care system. The Food and Drug Administration Amendment Acts of 2007 required the FDA to create a postmarket surveillance system to assess the safety of approved medical products. The Sentinel Initiative aims to enable the FDA to actively query electronic health record systems, administrative and insurance claims databases, and registries to evaluate possible medical product safety issues in a rapid and secure manner. The Sentinel system is still in development and has not yet facilitated rapid drug safety assessment or improved drug utilization. Although the FDA maintains that the Sentinel program holds promise for regulatory decisions on the basis of big data tools to organize and evaluate evidence and to maintain standards of safety and efficacy, alternative big data options are being explored. ASCO's big data initiative, CancerLinQ, represents a major effort in the development of an integrated real-time data resource for clinical oncology practice, quality performance assessment, and identification of safety concerns in a real-world setting. CancerLinQ also has the potential to contribute valuable information on biosimilar use and effectiveness.

INTERCHANGEABILITY, SWITCHING, AND SUBSTITUTION

A biosimilar is a biologic product that is highly similar to a specific reference biologic product. When a product is deemed biosimilar, there are no clinically meaningful differences between the reference biologic product and the product licensed as a biosimilar. Whereas there may be minor differences in the inactive compounds of

a biosimilar, the safety, purity, and potency of the product is highly similar to the reference biologic product. It is important to note that, unlike the relationship between generics and innovator brand products, the biosimilarity of a product is based on its similarity to the reference product and not to other biosimilars (Fig 1).

The biosimilarity and interchangeability of a product are determined after FDA review, whereas prescribing, dispensing, and the substitution of biologic products are regulated at the state level in a regulatory process that is similar to that of the dispensing and substitution of innovator drugs and generics. Generally, FDA approval of a biosimilar product is an indication that safety and efficacy are not meaningfully different from the reference product.

BPCIA allows substitution—the practice of dispensing an interchangeable product—to any given patient at the pharmacy level without consulting the prescriber. State laws generally uphold the authority of the physician to make final treatment decisions, including determinations of medical necessity and non-substitution. Although the FDA designation of interchangeable means that the biologic product may be substituted without the intervention of the prescribing provider, physicians and patients should be aware of potential product substitutions so that they can make informed treatment decisions.

For a biosimilar to be deemed interchangeable by the FDA, it has to be "expected to produce the same clinical result as the reference product in any given patient"[10(p3)] and fulfill necessary safety requirements as outlined by the FDA, including the evaluation of the safety and efficacy of switching back and forth between an interchangeable product and a reference product that will be administered more than once. When a product is deemed interchangeable, the data, analytics, and methodologies used to test and compare biosimilars with reference products provide scientific justification for expecting the same clinical outcomes.

Currently, no biosimilar has been approved by the FDA as being interchangeable with its reference product. State regulation, which relies on the federal determination, will dictate how and when biosimilars may be substituted for originator biologics. Regulations will vary from state to state and are currently in various stages of development.

NAMING, LABELING, AND OTHER REGULATORY CONSIDERATIONS

To ensure high-quality cancer care, oncologists, prescribers, patients, and pharmacists must be able to easily identify biologic products and ensure that patients receive the intended therapy. The complexity of biosimilars, including the manufacturing process, requires a naming and labeling scheme that is different from the naming and labeling of conventional drug products. At a basic level, oncologists must understand the significance of the name of each specific biosimilar that is being considered for use as treatment, as well as the clinical information associated with the biosimilar product.

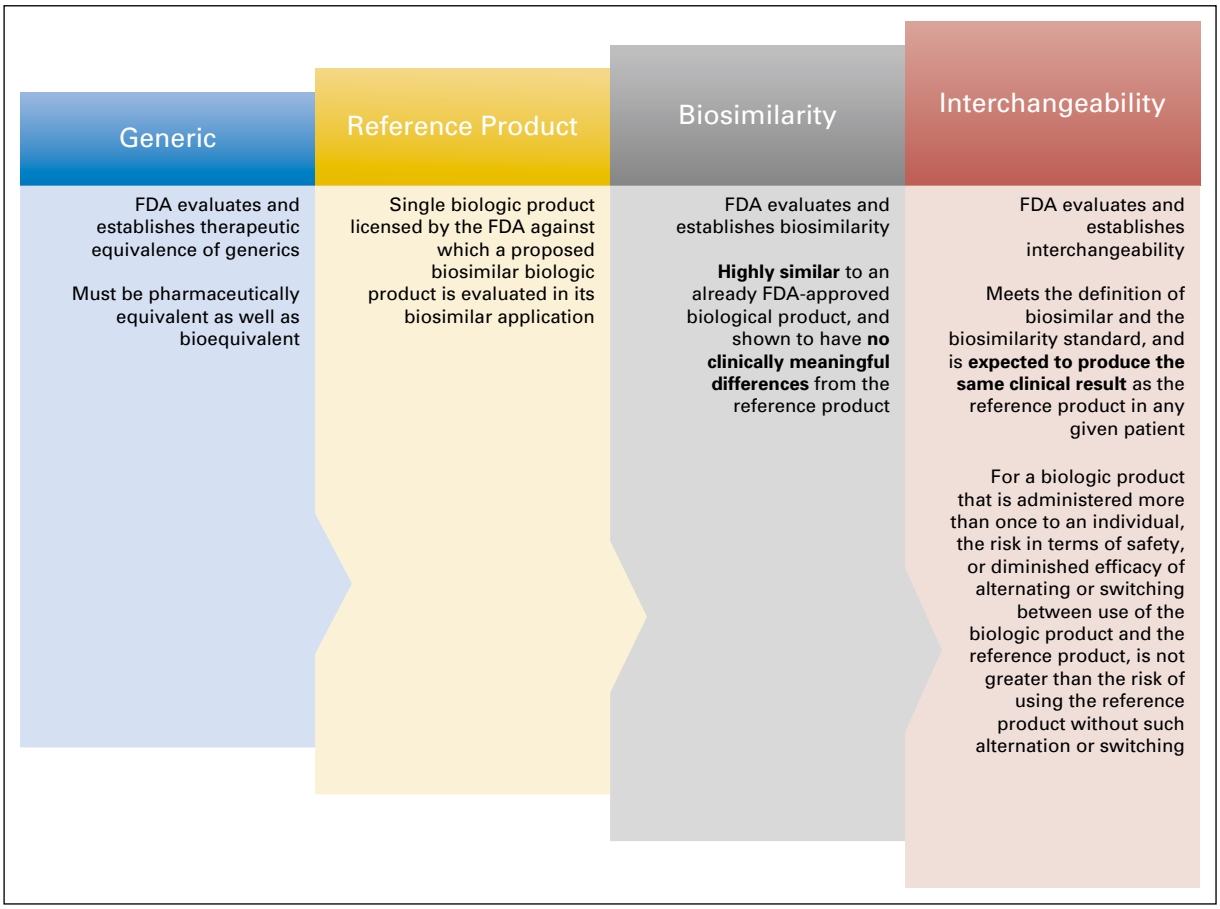

Fig 1. Definitions. FDA, US Food and Drug Administration.

Although physicians are familiar with the chemical and pharmacologic characteristics of drugs and biologics, the identification of the product is often associated with a single name that is universally recognized by providers, payers, and other clinicians. Thus, products are usually identified by a proper name that reflects the chemical and pharmacologic properties of a product or a proprietary/trademarked name. In the case of biosimilars, by definition, the products bear some differences that may warrant different clinical decisions (Table 1).

In its final guidance to the industry on the nonproprietary naming of biologic products, FDA guidance instructs manufacturers to assign a nonproprietary name that includes the core name of the product plus a distinguishing FDA-designated suffix that is devoid of meaning and composed of four lowercase letters.[11] The unique four lowercase-letter suffix affixed to a shared core name indicates a relationship among biologic products and is intended to be constant over time. As guidance on interchangeability has not been finalized, the FDA is continuing to consider the appropriate suffix format for interchangeable products.

Another aspect of providing optimal care and choosing the correct therapeutic product is the availability of accurate, scientific, and balanced information about the therapeutic characteristics of a product, which are included in the product labeling. Product labeling largely reflects the results of clinical studies that support the safety and efficacy of a product and may be used by providers to learn about the product and make clinical decisions. In the case of biosimilars, this information may also convey subtle, but important differences between the biosimilar and the reference biologic, including whether a biosimilar is interchangeable with the reference biologic.

The FDA has issued draft guidance on the proposed labeling requirements of biosimilar products.[12] Labels for biosimilars include a biosimilarity statement that describes the relationship to the reference product, (ie, Biosimilar X is biosimilar to Reference Product Y for the indications listed). The labels also include a footnote that defines the term, biosimilar, and indications and usage as well as adverse reactions and immunogenicity information. In the proposed guidance, the FDA maintains the presumption that the biosimilar designation is sufficient to support manufacturer claims of safety and efficacy. As such, merely citing the reference product in the labeling would be appropriate and could convey all necessary information for therapeutic decision making. However, in instances in which the indications, dosing, storage, etc, for a reference product and biosimilar may be different, statements that highlight these differences and additional details that explain the clinical aspects of these differences are necessary to facilitate the appropriate use of biosimilars. In addition, as the FDA continues to develop policies to designate the interchangeability of products, the inclusion of information related to interchangeability will be important. Distinction and clarity on the naming and labeling of biosimilar products before, during, and after use are critical to avoid unintended alternating or switching of biologic products that have not been deemed interchangeable by the FDA.

VALUE OF BIOSIMILARS: REIMBURSEMENT, COVERAGE, AND COST

Biosimilars have the potential to decrease the overall cost of care for complex medical conditions. Medicare, Medicaid, and commercial payers all have approached the reimbursement of biosimilars differently; however, it is clear that reasonable compensation, fair and medically appropriate coverage, and transparency of cost will serve to ensure a true value benefit to patients and society and promote access to new and innovative therapies.

BPCIA provides authority to the Centers for Medicare & Medicaid Services (CMS) to implement reimbursement policies for biosimilars. Many biologics and biosimilar products are reimbursed under a patient's medical benefit rather than the pharmacy benefit; therefore, CMS reimbursement for reference biologics is the same as that for all other drugs covered under Medicare Part B—that is, average sales price (ASP) plus a fixed percentage mark-up, which is currently 6% of the ASP, or ASP + 6%. As such, each reference biologic is given its own unique Healthcare Common Procedure Code.

Table 1. Selected Clinical and Pharmacologic Characteristics of Reference Agents and Selected Biosimilars in Development

Agent	Pharmacokinetics*	Target Binding Assay†	Cell Proliferation Assay‡	ORR§	Ratio of ORR¶	Vial Size, mg	Manufacturer
Trastuzumab (Herceptin; Genentech)[6,7]	Reference	Reference (HER2)	Reference	146 (64%) of 228	Reference	150 and 420	Genentech
Ogivri (trastuzumab-dkst)[7]	95.7 (89.7 to 101.5)	99.94 to 100.08	99.87 to 100.01	161 (70%) of 230	1.09 (0.98 to 1.22)	420	Mylan/Biocon
Bevacizumab (Avastin; Genentech)[8]	Reference	Reference (VEGF-A)	Reference	131 (42%) of 314	Reference	100 and 400	Genentech
Mvasi (bevacizumab-awwb)[9]	98.3 (94.0 to 102.9)	97.07 to 104.18	99.45 to 105.2	128 (39%) of 328	0.93 (0.8 to 1.09)	100 and 400	Amgen

Abbreviations: HER2, human epidermal growth factor receptor 2; ORR, overall response rate; VEGF-A, vascular endothelial growth factor A.
*The ratio of the measure of exposure (area under the plasma concentration-time curve from time 0 [predose] extrapolated to infinity [$AUC_{0-\infty}$] Geometric Mean Ratio with 90% CI) of the reference product divided by the AUC of the biosimilar after a single dose in healthy volunteers. For trastuzumab, 8 mg/kg; and for bevacizumab, 3 mg/kg. Equivalence is defined as including 100.
†90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.
‡90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.
§Trastuzumab with taxane breast cancer response at week 24, bevacizumab with carboplatin, and paclitaxel in non–small-cell lung cancer over six cycles.
¶90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.

Initially, CMS set reimbursement for biosimilars at the volume-weighted ASP of all biosimilar products within the same billing and payment code, plus an additional amount of 6% of the ASP of the reference product. The policy, which is similar to that for the reimbursement of multisource generics, was problematic for stakeholders, because the ASP of the reference biologic was not included in the weighted ASP of the biosimilars. However, beginning January 2018, for newly approved biosimilar products, biosimilars with a common reference product will no longer be grouped into the same billing code. CMS will code each biosimilar separately and reimburse at the current rate, which is ASP + 6%.

CMS also shares authority with states to regulate the coverage and reimbursement of drugs and biologics in the Medicaid program. The Medicaid program currently views biosimilars as single-source products and reimbursement methodologies reflect state-specific reimbursement for single-source products rather than methodologies that govern the reimbursement of multisource products. This means that each biosimilar may have a different reimbursement rate.

Commercial payers, including Medicare Part D plans, provide coverage for oral biologics under the pharmacy benefit of health insurance plans. Individual plan structure dictates the level of coverage and may also impose various cost-sharing and utilization management strategies in an effort to control costs. Such policies often result in higher out-of-pocket costs for single-source or nonpreferred products. On one hand, biosimilars and their relationship to biologics call for policies that are associated with generics that would tend to limit out-of-pocket costs; however, if a biosimilar is not interchangeable, it could stand alone as a single-source product and could therefore be subject to policies that are associated with single-source and nonpreferred products. ASCO principles for coverage and utilization management policies should be used to ensure the delivery of high-quality care that is most appropriate for patients while also ensuring patient access to medically necessary care.[13]

PRESCRIBER AND PATIENT EDUCATION

Given the novelty of biosimilar development in the United States and its reduced emphasis on clinical testing, there is greater need for education among providers regarding biosimilar products and their appropriate use. ASCO will continue to work to provide education that is focused on clarifying the difference between biosimilars and generic drugs; defining interchangeability, switching, and substitution; explaining naming and labeling issues; and emphasizing the need for postmarket safety surveillance. A broad range of educational materials, sources, and formats developed through a peer-review process, including appropriate conflict of interest provisions, must be readily available to all stakeholders (Appendix Table A1, online only). Practice guidelines for how biosimilars are prescribed, administered, and dispensed will be an important facet of educating oncologists.

Examples of such efforts include developing Webcasts, online practice guidelines, and social media updates potentially via ASCO University. Incorporating education sessions on biosimilars at scientific meetings, especially at the ASCO Annual Meeting as well as collaborating with ASCO's State Affiliates Council to elaborate and provide comparisons of the differing state prescribing regulations for biosimilars are needed. Education resources could be developed and maintained on ASCO's patient resource Web site and annual meeting repository, Cancer.net and ASCO's Meeting Library, respectively. Finally, ASCO's big data initiative, CancerLinQ, provides an opportunity to collect postmarket information on biosimilars that can be leveraged as real-time, rapid-learning educational tools in the health care setting.

For patients, the best source of patient education is the treating physician, regardless of the prescribed drug. However, as few resources exist that serve to educate patients on the use of biosimilar products, ASCO is committed to working with oncologists and other stakeholders to provide a wide range of educational materials tailored for patient use to facilitate patient understanding and acceptance of biosimilar products as appropriate treatment options.

The FDA has recently announced a series of educational Webinars designed to help health care professionals better understand FDA regulation and medication safety. The first Webinar is intended to provide an overview of the regulatory framework for biosimilar products, including the general requirements of the approval pathway for biosimilars and the approach and scientific concepts used by the FDA to review biosimilar products.

These educational materials—developed by professional societies and government entities in conjunction with patients or patient advocacy organizations—should provide all information relevant to the patient, including patient safety and efficacy concerns about biosimilars and any concerns regarding interchangeability and cost. These resources should be readily available for providers to share with patients in a timely manner and, when appropriate, to facilitate a dialog between the patient and the provider.

In conclusion, biosimilars will play an important role in the future care of patients with cancer and will improve access to valuable medicines. Whereas many biosimilars in oncology will be available in the next several years, their use and effect on patient care and health care costs will largely depend on patient and provider acceptance on the basis of an adequate understanding of the safety and efficacy of these agents in cancer care. This statement affirms ASCO's commitment to ensure the availability of biologics that are necessary in the delivery of high-quality, high-value care. To enhance patient and provider confidence in biosimilars, it is necessary to educate oncology providers and continue to advocate for federal and state policies that ensure the efficient approval, unrestricted access, and appropriate use of biosimilars.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. American Society of Clinical Oncology: The state of cancer care in America 2016. https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/2016-socca-report.pdf
2. Statista. Total global biologics spending from 2002 and 2017 (in billion U.S. dollars). https://www.statista.com/statistics/280578/global-biologics-spending
3. American Society of Clinical Oncology: Biosimilars. https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2013_biosimilars_Statement.pdf
4. Tabernero J, Vyas M, Giuliani R, et al: Biosimilars: A position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. ESMO Open 1:e000142, 2017
5. Friends of Cancer Research: The future of the U.S. biosimilar market: Development, education, and utilization. http://www.focr.org/sites/default/files/pdf/The%20Future%20of%20U.S.%20Biosimilars_0.pdf
6. Genentech: Herceptin product information. https://www.gene.com/download/pdf/herceptin_prescribing.pdf
7. US Food and Drug Administration: FDA Briefing Document FDA: Oncologic Drugs Advisory Committee Meeting—MYL-1401O, a proposed biosimilar to Herceptin (trastuzumab). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566369.pdf
8. Genentech: Avastin product information. https://www.gene.com/download/pdf/avastin_prescribing.pdf
9. US Food and Drug Administration: FDA Briefing Document Oncologic Drugs Advisory Committee Meeting—ABP215, a proposed biosimilar to Avastin (bevacizumab). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566365.pdf
10. US Food and Drug Administration: Patient Protection and Affordable Care Act. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf
11. US Food and Drug Administration: Nonproprietary naming of biological products: Guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf
12. US Food and Drug Administration: Labeling for biosimilars products: Guidance for industry. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf
13. American Society of Clinical Oncology: American Society of Clinical Oncology policy statement on the impact of utilization management policies for cancer drug therapies. J Oncol Pract 13:758-762, 2017

Affiliations

Gary H. Lyman, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA; **Edward Balaban**, University of Pennsylvania Medical College, Philadelphia, PA; **Michael Diaz**, Florida Cancer Specialists and Research Institute, St Petersburg, FL; **Andrea Ferris**, Lungevity Foundation, Bethesda, MD; **Anne Tsao**, The University of Texas MD Anderson Cancer Center, Houston, TX; **Emile Voest**, The Netherlands Cancer Institute, Amsterdam, the Netherlands; **Robin Zon**, Michiana Hematology Oncology, Mishawaka, IN; **Michael Francisco**, **Sybil Green**, **Shimere Sherwood**, and **Richard L. Schilsky**, American Society of Clinical Oncology, Alexandria, VA; and **R. Donald Harvey**, Emory University School of Medicine, Atlanta, GA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

American Society of Clinical Oncology Statement: Biosimilars in Oncology

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Gary H. Lyman
Leadership: Generex Biotechnology
Consulting or Advisory Role: Halozyme, G1 Therapeutics, Coherus Biosciences, Mylan
Research Funding: Amgen (Inst)

Edward Balaban
No relationship to disclose

Michael Diaz
Employment: Florida Cancer Specialists
Leadership: Florida Cancer Specialists
Stock or Other Ownership: Florida Cancer Specialists
Consulting or Advisory Role: Janssen Pharmaceuticals

Andrea Ferris
No relationship to disclose

Anne Tsao
Honoraria: Novartis, Boehringer Ingelheim, AstraZeneca, Genentech, Bristol-Myers Squibb, Epizyme, EMD Serono, ARIAD Pharmaceuticals, Imedex, Eli Lilly, Novartis
Consulting or Advisory Role: Novartis, Boehringer Ingelheim, Astellas Pharma, Genentech, MedImmune, Imedex, Eli Lilly, Bristol-Myers Squibb, Epizyme, AstraZeneca, ARIAD Pharmaceuticals, EMD Serono
Research Funding: MedImmune (Inst), Merck (Inst), Genentech (Inst), Seattle Genetics, Millennium Pharmaceuticals, Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Polaris

Emile Voest
Consulting or Advisory Role: InteRNA, Biogeneration Ventures
Research Funding: Novartis (Inst), GlaxoSmithKline (Inst), Genentech (Inst), Pfizer (Inst), AstraZeneca (Inst), Eisai (Inst), Pfizer (Inst), Bristol-Myers Squibb (Inst), Merck (Inst)

Robin Zon
Consulting or Advisory Role: Medical Protective Malpractice Insurance Company
Research Funding: Agendia (Inst)
Other Relationship: Medical Protective Advisory Board

Michael Francisco
No relationship to disclose

Sybil Green
No relationship to disclose

Shimere Sherwood
No relationship to disclose

R. Donald Harvey
No relationship to disclose

Richard L. Schilsky
Research Funding: AstraZeneca (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Genentech (Inst), Eli Lilly (Inst), Merck (Inst), Pfizer (Inst)

Acknowledgment

We thank the FDA for their guidance and support in the development of this paper.

Appendix

Table A1. Terminology

Term	Equivalence Determination	Definition	Reference Product (comparison)	Substitution Statute*	MD-Initiated Change†	Pharmacist-Initiated Change‡	Source§
Generic	FDA evaluates and establishes the therapeutic equivalence of generics	Must be pharmaceutically equivalent and bioequivalent	Innovator brand: All products deemed equivalent to a brand may also be deemed equivalent to other therapeutic equivalents	State-regulated authorization of generic substitution	Yes	Yes, in most states	Orange book
Reference Product		Single licensed biologic product against which a biologic product is evaluated in a 351(k) application					
Biosimilar	FDA evaluates and establishes biosimilarity	Highly similar to an already FDA-approved biologic product, and shown to have no clinically meaningful differences from the reference product	Reference biologic: Biosimilars are deemed biosimilar to the reference product only		Yes	No	Purple book
Interchangeable	FDA evaluates and establishes interchangeability	Meets the definition of biosimilars and the biosimilarity standard, and is expected to produce the same clinical result as the reference product in any given patient for a biologic product that is administered more than once to an individual, and the risk in terms of safety, or diminished efficacy of alternating or switching between use of the biologic product and the reference product, is not greater than the risk of using the reference product without such alternation or switching	Reference biologic: Interchangeability of a product indicates interchangeability with the reference biologic only	BPCIA; FDA-deemed interchangeable products may be dispensed in place of the reference product	Yes	Yes	Purple book

Abbreviations: BPCIA, Biologics Price Competition and Innovation Act; FDA, US Food and Drug Administration.
*Varies from state to state.
†The physician may always choose which products to prescribe, administer, or dispense to the patient. Product selection is not regulated by any federal or state body, but rather reflects the physician's judgement regarding which product will result in desired outcomes—that is, physicians may use data, FDA determinations, etc, to understand equivalence and expected clinical outcomes.
‡The most-restrictive states prohibit any substitution without express consent of the physician. The least-restrictive states mandate substitution if there is an FDA-approved therapeutic equivalent. Most states require patient notification in any situation in which a product is substituted.
§The orange book does not establish substitution.