

AACE/ACE POSITION STATEMENT ON THE USE OF FOLLOW-ON BIOLOGICS AND BIOSIMILARS FOR ENDOCRINE DISEASES

*Vivian A. Fonseca, MD, FACE, Chair¹; Zachary T. Bloomgarden, MD, MACE²;
Samuel Dagogo-Jack, MD, DM, FRCP, FACE³; George Grunberger, MD, FACP, FACE⁴;
Daniel Einhorn, MD, FACP, FACE⁵; Alan J. Garber, MD, PhD, FACE⁶;
Yehuda Handelsman, MD, FACP, FNLA, FACE⁷; Irl B. Hirsch, MD⁸;
Guillermo E. Umpierrez, MD, FACP, FACE⁹*

This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position and consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

Abbreviations:

BPCIA = Biologics Price Competition and Innovation Act; **FDA** = Food and Drug Administration; **FFDC** = Federal Food Drug and Cosmetics Act; **PHS** = Public Health Services Act; **TE** = therapeutic equivalence

INTRODUCTION

In the past decade, the federal regulatory landscape regarding large complex molecules known as biologics has experienced great change. It is important for clinicians to recognize the differences between prescriptions for biologics and generics.

In 2010, the United States Congress passed a law to create an approval pathway for drugs defined as biosimilar, and the Food and Drug Administration (FDA) has released draft guidance to determine whether those biosimilars are interchangeable with their reference products (1,2). The FDA has also approved follow-on biologics through a separate statute including a recently marketed follow-on insulin product (3). The following introduces the vocabulary the federal government uses for various biologic products, describes the multiple pathways a follow-on biologic may use to come to market and how that could affect the ability of a physician to ensure their patient is receiving the therapy they have prescribed for that patient.

The development and availability of biologics is very relevant to clinicians in endocrinology. Multiple endo-

Submitted for publication June 22, 2017

Accepted for publication July 9, 2017

From the ¹Professor of Medicine and Pharmacology, Tullis Tulane Alumni Chair in Diabetes, Chief, Section of Endocrinology Tulane University Health Sciences Center, New Orleans, Louisiana, ²Clinical Professor, Mount Sinai School of Medicine, Editor, the *Journal of Diabetes*, New York, New York, ³A.C. Mullins Professor & Director, Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, Memphis, Tennessee, ⁴Grunberger Diabetes Institute, Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine, Bloomfield Hills, Michigan, ⁵Professor of Medicine, Chief, Diabetes Division, University of Texas Health Science Center at San Antonio, San Antonio, Texas, ⁶Professor, Departments of Medicine, Biochemistry and Molecular Biology, and Molecular and Cellular Biology,

Baylor College of Medicine, Houston, Texas, ⁷Medical Director & Principal Investigator, Metabolic Institute of America, President, American College of Endocrinology, Tarzana, California, ⁸Professor of Medicine, University of Washington School of Medicine, Seattle, Washington, and ⁹Professor of Medicine, Emory University School of Medicine, Director, Endocrinology Section, Grady Health System, Atlanta, Georgia.

Address correspondence to Dr. Vivian A. Fonseca, Tulane University Medical Center, 1430 Tulane Avenue, Slip 53, New Orleans, LA 70112.

E-mail: vfonseca@tulane.edu.

Published as a Rapid Electronic Article in Press at <http://www.endocrinepractice.org>. DOI: 10.4158/EP-2017-0052

To purchase reprints of this article, please visit: www.aace.com/reprints.

Copyright © 2017 AACE.

This material is protected by US copyright law. To purchase commercial reprints of this article, visit www.aace.com/reprints. For permission to reuse material, please access www.copyright.com or contact the Copyright Clearance Center, Inc. (CCC).

crine-indicated biologics are already being marketed, and more are sure to be approved. As the number of biosimilar or follow-on biologics grows, patients may see a disruption in continuity of care, and physicians will need to understand exactly what it means to prescribe comparable biologics. In 2016, the American Association of Clinical Endocrinologists convened a task force to provide guidance on the topic for endocrinologists and other clinicians in order to achieve optimal clinical care without disruption.

“Biologics” include a category of medical preparations derived from living organisms (4). Unlike small-molecule drugs that are easily replicated through a well-understood chemical process, biologics are complex treatments that require sophisticated biotechnologies and manufacturing technologies to develop, making it far more difficult to produce a “generic” version of a biologic (5). Competing, similarly structured biologics are not described as “generic,” instead manufacturers, regulatory agencies, and others use the terms “follow-on biologic” or “biosimilar” (6).

BIOSIMILAR VERSUS FOLLOW-ON BIOLOGIC

When used outside of a regulatory context, the terms “follow-on biologic” and “biosimilar” may be used interchangeably. Follow-on protein is an informal term used by the FDA to describe a product that is intended to be sufficiently similar to a biologic product already approved by the FDA to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the already approved biologic product (7). A product that may use the legal label of biosimilar must be approved through a specific pathway. Use of either term should not be understood to mean that the follow-on or biosimilar is interchangeable with the reference product. The differences in terminology can be found in the regulatory history of the drug-approval process.

There are two laws that have jurisdiction over the approval of biologic medicines in the United States. The first is the Federal Food Drug and Cosmetics Act (FFDC); the other is the Public Health Services Act (PHS) (8,9). Most biologics are subject to approval provisions of the PHS, which includes an additional focus to system controls for the manufacturing process. Most biologics are required to apply for approval through a PHS section 351 Biologics License Application (BLA); however, there is a subset of biologics, including insulin, that do not require approval through a PHS pathway and instead receive approval through a FFDC section 505 New Drug Application.

Until 2010, there was no pathway for biologics approved under the PHS to receive approval as a follow-on. Follow-on biologics under the jurisdiction of the FFDC 505 pathway (as opposed to PHS 351) could rely on the 505(b)(2) abbreviated approval pathway. Examples of drugs that are 505(b)(2)-approved follow-on biologics include Omnitrope (somatropin for injection), Fortical

(calcitonin-salmon), and GlucaGen (glucagon injection), which received approval in 1998 and was one of the first 505(b)(2) follow-on proteins (10-12).

The standard of evaluation for 505(b)(2) follow-on proteins is proof of “safety and effectiveness.” Proof of safety and efficacy are determined on a case-by-case basis. Applicants under 505(b)(2) may refer to safety and effectiveness studies of previously approved listed drugs so long as it is scientifically justifiable. Scientific justification includes proof that the follow-on product is highly similar to the listed product. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data, including clinical or nonclinical data, as appropriate to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness (13).

In 2010, as part of the Affordable Care Act, the U.S. Congress signed into law the Biologics Price Competition and Innovation Act (BPCIA). The BPCIA directed the FDA to develop an abbreviated approval pathway, similar to those found in section 505 of the FFDC, for biologics approved under the PHS. Further, the pathways are to identify follow-on biologics as either “biosimilar” or “interchangeable.” The BPCIA defines biosimilar to mean “(A)...highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B)...no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” There are currently only draft FDA guidance on requirements to establish interchangeability, with final guidance expected this year. The FDA approved Zarxio (filgrastim-sndz), the first ever “biosimilar” approved in the U.S., in March 2015 (1,2,14).

The biosimilar pathway was codified as section 351(k) of the PHS. Unlike a 505(b)(2) follow-on, biosimilars are to be evaluated for “no clinically meaningful differences between the biological product and the reference product.” Like a 505(b)(2) follow-on, a biosimilar may rely on data from a reference product and will be required to supplement that data with clinical studies sufficient to demonstrate safety, purity, and potency. The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis. The FDA encourages manufacturers to work with the appropriate divisions at the FDA to obtain input on proposed development plans (15).

As of March 23, 2020, these distinctions will be null. The BPCIA included the provision that “an approved application for a biological product under section 505 of the [FFDC] shall be deemed to be a license for the biological product under such 351 [of the PHS Act] on the date that is 10 years after the date of enactment of [BPCIA].” In other words, all FFDC-approved biologics will fall under the scope of the PHS, and the 505(b)(2) pathway

will no longer be available for follow-on protein approval. Furthermore, applications for biological products that have already been approved under 505(b)(2) will be treated as a BLA under section 351(k) and will adopt the “biosimilar” terminology (9,16).

INTERCHANGEABILITY AND SUBSTITUTION

Prior to the enactment of the BPCIA, the FDA had no formal definition for the term interchangeability. Informally, the agency used it to mean either a drug that is a therapeutic equivalent, and thus could potentially be substituted at the pharmacy level without a physician’s intervention, or the term described “similar products that are not ‘substitutable’ but which, under a physician’s supervision, could be used to treat the same disease or condition in the same patient.” The term interchangeable has since gained a statutory definition as it relates to biologics and biosimilars approved under the BPCIA; however, pharmacist substitution of FFDC-approved follow-on proteins is governed by the same therapeutic equivalence rules as small-molecule drugs (7).

The BPCIA allows that biosimilars may be interchangeable if the information submitted in a 351(k) application demonstrates both biosimilarity *and* meets additional standards. Interchangeability requires a demonstration that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient and, when applicable, that “the risk in terms of safety or diminished efficacy of alternating or switching between use of the [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch.” The FDA has released draft guidance to industry on how interchangeability may be demonstrated but has not finalized that document; there are currently no FDA-approved interchangeable biosimilars. The FDA has created a reference guide called the ‘Purple Book’ which lists PHS-licensed biological products with information regarding biosimilarity and interchangeability (2,6,17).

The FFDC allows drugs to be listed as generic through a process that assigns therapeutic equivalence (TE) ratings via a demonstration of “sameness.” The FDA publishes TE ratings in a reference guide called the ‘Orange Book,’ which is used by, among other parties, pharmacists and payers to determine whether a generic product may be substituted for an innovator product. If a product is awarded a TE rating beginning with the letter A, it is generally considered safe for substitution. A TE rating beginning with the letter B indicates outstanding questions regarding equivalence data and may not be substituted. There is some legal ambiguity regarding FDA’s ability to assign TE ratings to biologics approved under the 505(b)(2) pathway. The FDA position, generally, regarding 505(b)(2) drugs is that it may assign TE using the same criteria with which it evaluates other generic drug applications (so-called 505(j)

drugs). Two current examples of 505(b)(2) drugs that have been assigned a TE rating include multiple versions of AndroGel 1% testosterone gel. The Perrigo topical testosterone was assigned an AB TE rating as it related to AndroGel and may be substituted by pharmacists (subject to state pharmacy rules). Conversely, the Teva topical testosterone was assigned a BX TE rating because the bioequivalence data submitted were insufficient; therefore, it is not considered substitutable (18).

However, it should be noted that topical testosterone is a small-molecule drug, and its TE is similar to the way the FDA would evaluate a 505(j) generic and not a follow-on biologic. Unlike 505(b)(2) small-molecule drugs, two biologics are necessarily incapable of meeting the “duplicate” standard applied to small-molecule generics. Therefore, it is unlikely that the FDA, by their own standard, would be capable of approving TE for a 505(b)(2) biologic. If a biologic were to receive a TE rating, the FDA has not made it clear how it will treat that drug once it is converted to a 351k biosimilar drug in 2020 (18).

Substitution rules are not exclusively determined by the FDA. State pharmacy boards or regulatory agencies also provide rules regarding a pharmacist’s ability to substitute equivalent or interchangeable drugs, and each state uses different rules to establish their pharmaceutical substitution formularies. Broadly, a pharmacist will rely on the Orange Book as well as supplemental literature to make substitution determinations (19).

Biosimilar substitution has presented new questions for state legislatures and pharmacy boards. Many states are writing new regulations regarding the way their pharmacists should handle biosimilars. Generally speaking, states are requiring a finding of interchangeability by the FDA. Other, less universal, features of state biosimilar substitution legislation are:

- allow a prescriber to require pharmacists dispense as written;
- require the pharmacists notify or communicate to the prescriber that a substitution has occurred;
- require patient notification that a change has been made; and
- include reference to the Orange Book, or TE, ensuring protection for patients prescribed FFDC biologics.

Currently no biosimilar has been deemed interchangeable by the FDA and would not be eligible for substitution by pharmacists in any state. The 505(b)(2) follow-on biologics have the option of applying for a therapeutic rating to permit substitution, but the process is complex, and thus far, TE AB ratings have only been awarded to small-molecule 505(b)(2) drugs. If a physician (or other prescriber) is concerned with substitution, they may consult either the Orange or Purple book to confirm the FDA position on substitution and should also review their state’s rules on the topic (20).

FDA DRAFT GUIDANCE FOR INTERCHANGEABILITY OF BIOSIMILARS

In January 2017, the FDA released the draft guidance document “Considerations in Demonstrating Interchangeability with a Reference Product” (Draft Guidance). The Draft Guidance, intended to assist biologic product sponsors in demonstrating interchangeability with reference products, is not binding on the FDA but expresses its current thinking on the topic of 351(k) biosimilar interchangeability.

The Draft Guidance discusses 4 issues related to the demonstration of interchangeability. These include:

1. Data and information needed to support a demonstration of interchangeability.
2. Considerations for the design and analysis of a switching study or other relevant studies.
3. Recommendations regarding the use of a U.S.-licensed reference product in interchangeability studies.
4. Analysis of the proposed presentations of proposed interchangeable products.

The Draft Guidance applies more rigorous standards to interchangeability than those required for a 351(k) “biosimilar” designation but leaves a number of questions open (2).

CLINICAL APPLICATION OF CURRENT RULES

When a physician determines that the best course of treatment for a patient is to prescribe a biologic, there are a number of things that physician may need to evaluate. For example, suppose a physician is treating an insulin-naïve adult with type 1 diabetes and determines the best treatment is the long-acting human insulin analogue, insulin glargine. Insulin glargine is, by definition, a biologic, but how was it approved and in what ways should that inform the physician’s behavior when prescribing?

There are currently two FDA-approved versions of insulin glargine: Basaglar and Lantus. Lantus was approved for marketing using the FDCA 505(b)(1) pathway, meaning it submitted a full application in the year 2000. Lantus was approved under the FDCA pathway, as opposed to the BPCIA, because insulin fits into a narrow category of biologics approved prior to enactment of the PHS. Basaglar, using information from the Lantus application, as well as supplemental studies indicating safety and efficacy, was approved using the 505(b)(2) pathway and is definitionally a follow-on biologic. Basaglar is not a biosimilar, is not bioidentical, or interchangeable with Lantus; however, it may be equally appropriate for this particular patient.

Knowing that these two biologics were approved using a FDCA pathway means that TE is rated in the FDA Orange Book (PHS biologics equivalence is found in the Purple Book), so a physician would consult the Orange Book to

find that Basaglar does not have a TE rating in reference to Lantus. This means that a pharmacist is unlikely to switch one drug for another without consulting the prescriber, as most state pharmacy laws require the pharmacist to rely on the Orange Book for a decision to switch one prescription for another.

A prescribing physician should also be mindful of how a patient’s insurance formulary treats these comparable treatments. A formulary will consider whether one treatment may be substituted for another and make a decision to cover just one of the two. In those circumstances, a physician may need to prescribe the preferred insulin glargine as “dispense as written,” and insurers that exclusively cover one treatment will need an explanation of medical necessity to cover the other. Ultimately, the physician should discuss these concerns with the patient and make a decision based on the treatment plan best suited for that patient. Unfortunately, no data exist on differences in adverse effects, making such a discussion theoretical.

CONCLUSION

As a growing number of follow-on biologic or biosimilar drugs make their way to the market, prescribing physicians should understand how regulators, pharmacists, and payers may affect delivery of these complex molecules to their patients. A biosimilar or follow-on biologic is necessarily not interchangeable with its reference product, though eventually these drugs may be deemed interchangeable through a forthcoming approval pathway. Without the proper designation in the FDA’s Purple or Orange book, a pharmacist is not likely to make a substitution, and a growing number of state laws are currently being enacted to ensure that no biosimilar substitution is made without first contacting the prescribing physician. Physicians should be aware that drug formularies will treat biosimilars as substitutable, at which point physicians should work with their patients to determine a course of treatment best suited to the patient’s unique condition.

ACKNOWLEDGMENT

We thank Michael Williams, JD, AACE Counsel and Manager of Healthcare Regulatory Policy, for medical writing assistance.

DISCLOSURE

AACE recognizes the importance of providing continued education to its members, which may require financial support from an outside entity through unrestricted educational grants. Outside support will not be used for the development and/or writing of AACE consensus statements/conference proceedings, white papers, or guidelines. Outside support may be accepted for the administration/logistical support of a consensus conference and for the

dissemination and distribution of the final written paper. The content of these documents is developed solely by AACE members and, as always, will remain free of any outside entity influence.

Dr. Fonseca reports that he is a consultant for Takeda, Novo Nordisk, Sanofi, Eli Lilly, Pamlabs, AstraZeneca, Abbott, Boehringer Ingelheim, Janssen, and Intarcia. He is also a speaker for Takeda, AstraZeneca, and Sanofi. Dr. Fonseca has received research grants from Novo Nordisk, Asahi, Eli Lilly, Abbott, Endo Barrier, Bayer, and Gilead.

Dr. Bloomgarden reports that he is a consultant for AstraZeneca, Intarcia, Johnson & Johnson, Merck, and Novartis. He is also a speaker for AstraZeneca, Johnson & Johnson, and Merck. Dr. Bloomgarden is also a shareholder in Allergan, Novartis, Pfizer, and Zimmer Biomet.

Dr. Dagogo-Jack reports that he has clinical research contracts with University of Tennessee, as well as AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. He is also a consultant for Janssen, Merck and Sanofi, and is a shareholder in Dance Pharma and Janacare.

Dr. Grunberger has no multiplicity of interest to disclose.

Dr. Einhorn reports that he is a consultant for Adocia, Eli Lilly, Novo Nordisk, and Sanofi.

Dr. Garber reports that he is a consultant for Novo Nordisk.

Dr. Handelsman reports that he has received research grants from Amgen, AstraZeneca, Bristol-Myers-Squibb, Boehringer Ingelheim, Grifols, Janssen, Lexicon, Merck, Novo Nordisk, and Sanofi. He is also a consultant for Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Eisai, Intarcia, Lilly, Janssen, Merck, Merck-Pfizer, Novo Nordisk, Regeneron, and Sanofi. Dr. Handelsman also serves on the speakers bureau for Amarin, Amgen, AstraZeneca, BI-Lilly, Janssen, Merck, Novo Nordisk, Regeneron, and Sanofi.

Dr. Hirsch reports that he is a consultant for Abbott Diabetes Care, Adocia, Big Foot, Intarcia and Roche.

Dr. Umpierrez reports that he received grant support to Emory University from AstraZeneca, Novo Nordisk and Sanofi.

REFERENCES

1. Patient Protection and Affordable Care Act, 2010. 42 U.S.C. 18001 §7002 "Approval pathway for biosimilar biological products." Available at: <https://www.congress.gov/111/plaws/publ148/PLAW-111publ148.pdf>. Accessed March 28, 2017.
2. **U.S. Food and Drug Administration.** *Considerations in Demonstrating Interchangeability With a Reference Product: Guidance for Industry – Draft Guidance.* January 2017. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>. Accessed March 28, 2017.
3. **U.S. Food and Drug Administration.** *FDA Approves Basaglar, the First "Follow-on" Insulin Glargine Product to Treat Diabetes.* December 16, 2015. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm>. Accessed March 28, 2017.
4. **U.S. Food and Drug Administration.** *Frequently Asked Questions About Therapeutic Biological Products.* Question 1. Available at: <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm>. Accessed March 28, 2017.
5. **Johnson J.** *Biologics and Biosimilars: Background and Key Issues* (CRS Report R44620; 2016). Retrieved from Congressional Research Service. Available at: <https://fas.org/sgp/crs/misc/R44620.pdf>. Accessed March 28, 2017.
6. **U.S. Food and Drug Administration.** *Information for Consumers (Biosimilars).* 2015. Available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm>. Accessed March 28, 2017.
7. **Woodcock J.** *Follow-on Protein Products.* Testimony before the House Committee on Oversight and Government Reform; March 2007. Available at: <https://www.fda.gov/NewsEvents/Testimony/ucm154070.htm>. Accessed March 28, 2017.
8. Federal Food Drug and Cosmetic Act, 21 U.S.C. 355.
9. Public Health Services Act, 42 U.S.C. 262.
10. **U.S. Food and Drug Administration.** Approval letter from FDA to Sandoz Inc. Re: Omnitrope. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021426s000_APPROV.pdf. Accessed March 28, 2017.
11. **U.S. Food and Drug Administration.** Approval letter from FDA to Unigene Laboratories, Inc. Re: Fortical. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021406s000_APPROV.pdf. Accessed March 28, 2017.
12. **U.S. Food and Drug Administration.** Approval letter from FDA to Novo Nordisk Pharmaceuticals, Inc. Re: Glucagen. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020918s000_Glucagen_AP_LTR.pdf. Accessed March 28, 2017.
13. **U.S. Food and Drug Administration.** (1999) *Guidance for Industry: Applications Covered by Section 505(b)(2).* Available at: <https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf>. Accessed March 28, 2017.
14. **U.S. Food and Drug Administration.** (2015). *FDA Approves First Biosimilar Product Zarxio.* Available at: <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm>. Accessed March 28, 2017.
15. **U.S. Food and Drug Administration.** (2015). *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry.* Available at: <https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf>. Accessed March 28, 2017.
16. **U.S. Food and Drug Administration.** (2016). *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009: Guidance for Industry – Draft Guidance.* Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf>. Accessed March 28, 2017.
17. **U.S. Food and Drug Administration.** *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations.* Available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>. Accessed March 28, 2017.
18. **U.S. Food and Drug Administration.** *Response to Abbott Laboratories, Inc./AbbVie Citizen Petition regarding therapeutic equivalence for a drug approved under section 505(b)(2).* July 23, 2014. Docket Nos. FDA-2011-P-0610 and FDA-2013-P-0371. Available at: <https://www.regulations.gov/document?D=FDA-2011-P-0610-0010>. Accessed March 29, 2017.
19. *State Regulations on Generic Substitution.* April 2009. Available at: <http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&segment=1186&dd=220901&AspxAutoDetectCookieSupport=1>. Accessed March 31, 2017.
20. **National Conference of State Legislatures.** *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars.* March 16, 2017. Available at: <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>. Accessed September 12, 2017.