SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES

Biosimilars: A Regulatory Overview

Michael S. Reilly, Esq.
Executive Director, Alliance for Safe Biologic Medicines

Presented at the Chapman University School of Pharmacy
May 29, 2015

About The Alliance for Safe Biologic Medicines (ASBM)

Harry L. Gewanter, MD, FAAP, FACR: Chairman, pediatric rheumatologist.

Philip Schneider: Dean, University of Arizona College of Pharmacy- Advisory Board Chair.

Organization formed in 2010.

- Steering Committee composed of patient and physician groups.
- Advisory Board comprised of physicians, researchers, pharmacists, and patients.

“The Four Pillars”

ASBM’S GUIDING PRINCIPLES

PRIORITIZING PATIENT SAFETY

LEVERAGING WHAT WE HAVE LEARNED

PROMOTING PHARMACO-VIGILANCE

KEEPING HEALTHCARE PROVIDERS RELEVANT

Recent ASBM Activity

October 2014: Present country-specific European survey results to Italian Health Ministry in Rome.

November 2014: Present country-specific European survey results to Spanish Health Ministry in Madrid.

December 2014: Present Comparative EU country data at DIA Conference in Berlin; Reveal Canadian survey results at Health Canada Biosimilars Forum.

February 2015: Survey of 400 U.S. Physicians on issue of transparency in biosimilar labeling.

March 15, 2015: The week following FDA approval of first biosimilar, ASBM's Dr. Gewanter and Dr. Schneider led a five-hour continuing education course for 125 pharmacists.

April 13, 2015: Dr. Gewanter and Dr. Schneider participated in 60th WHO Consultation on International Nonproprietary Names.

May 9, 2015: Conducted educational course on biosimilars for 140 Pharmacists who work for a manufacturer of biologics and biosimilars.

Biosimilars: U.S. Regulatory Background

Europe Has Led the Way on Biosimilars

- Biosimilar pathway established 2003.
- First biosimilar approved in 2006.
- To date EMA has approved 19 biosimilars that copy eight medicines.
- Approximately 15- 30% Markdown.

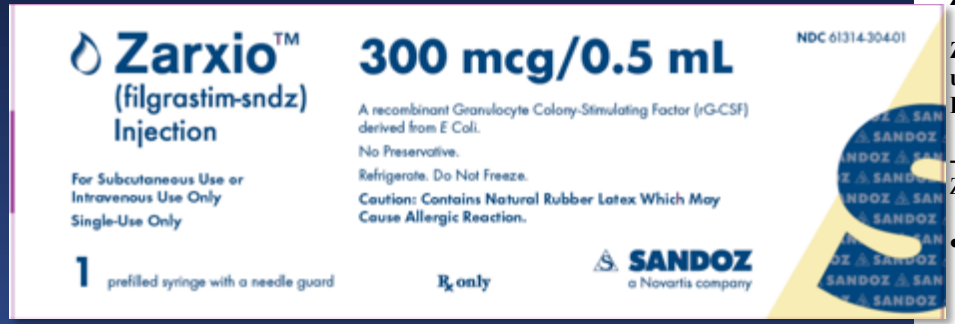
Biosimilars: How to Bring Them to the U.S.?

- For years, lawmakers on Capitol Hill had discussed how and when to bring biosimilars to the U.S. market.
- It was always understood that biologics were distinctly different from chemical medicines, and that biosimilars are fundamentally different from generic versions of chemical drugs.
- Biologics are not covered under the 1984 Hatch-Waxman Act for generic versions of conventional drugs.

The USA is Now Beginning to Catch Up with Europe…

March 6: First Biosimilar Approved

- *Zarxio (filgrastim-sndz)*



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZARXIO safely and effectively. See full prescribing information for ZARXIO.

ZARXIO™ (filgrastim-sndz) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
ZARXIO is a leukocyte growth factor indicated to:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral

The ACA Creates a U.S. Biosimilars Approval Pathway

- On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act that included a pathway for the approval of biosimilars—also referred to as the Biologics Price Competition and Innovation Act (BPCIA).

TITLE VII—IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES

Subtitle A—Biologics Price Competition and Innovation

SEC. 7001. SHORT TITLE.

(a) IN GENERAL.—This subtitle may be cited as the "Biologics Price Competition and Innovation Act of 2009".

(b) SENSE OF THE SENATE.—It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act

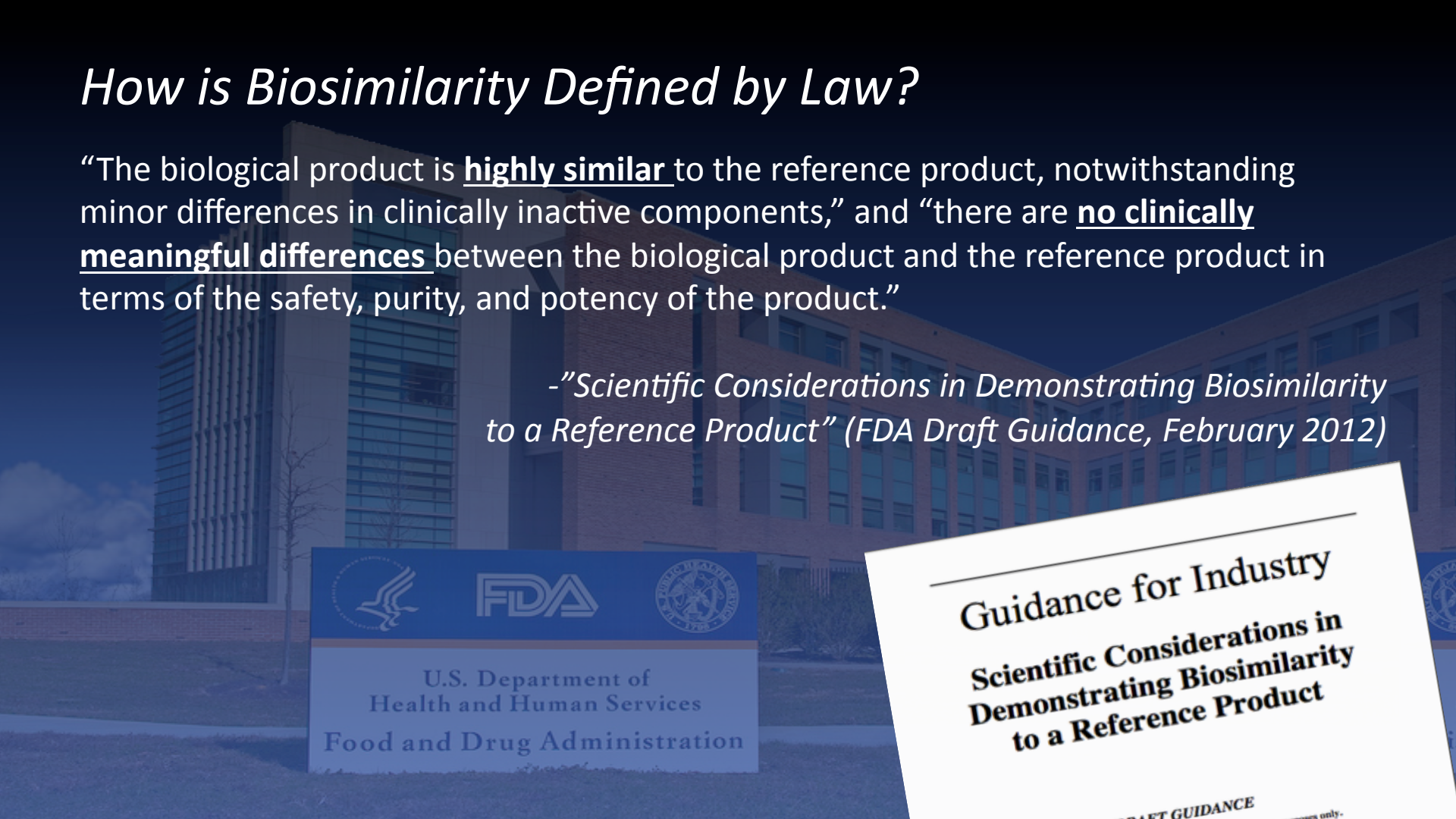
Congress Gave Broad Authority to the FDA to Determine How Biosimilars Will Be Approved

- In November 2010, the Food and Drug Administration (FDA) began consulting with patient groups, physicians, and industry leaders on how to approve the first copies of biologics, known as follow-on biologics or biosimilars.
- ASBM was formed in late 2010 to be a part of this dialogue.
- ASBM submitted its first formal comments December 30, 2010.

How is Biosimilarity Defined by Law?

"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."

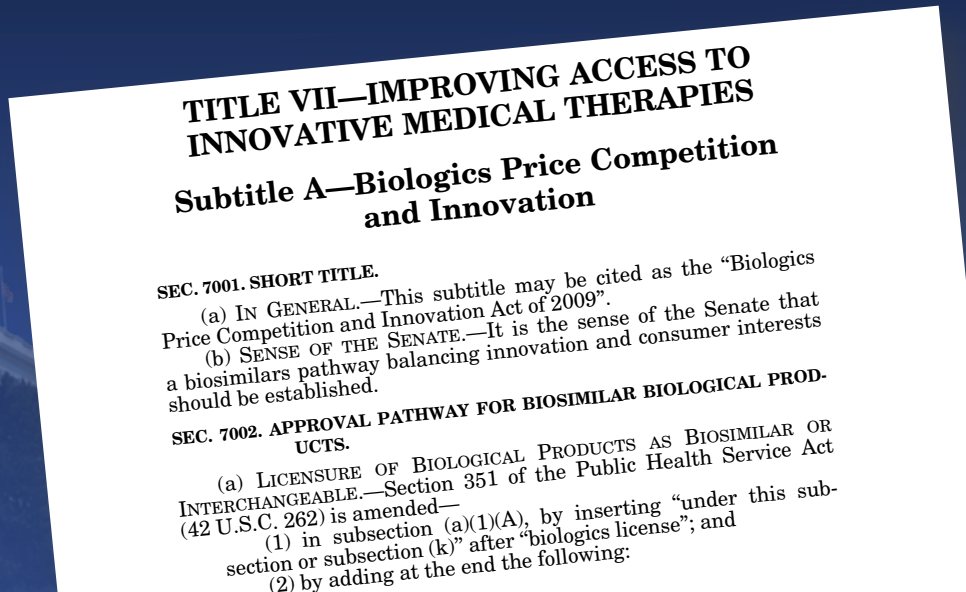
-"Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (FDA Draft Guidance, February 2012)



How is Interchangeability Defined?

Biologics Price Competition and Innovation Act,
Section (351)(k)(4)

- Be biosimilar to the reference product;
- Be expected to produce the same clinical result as the reference product in any given patient; and,
- If the product will be administered more than once to a patient, the risk (in terms of safety or diminished efficacy) associated with switching between the product and the reference product cannot be greater than the risk of repeated use of the reference product.



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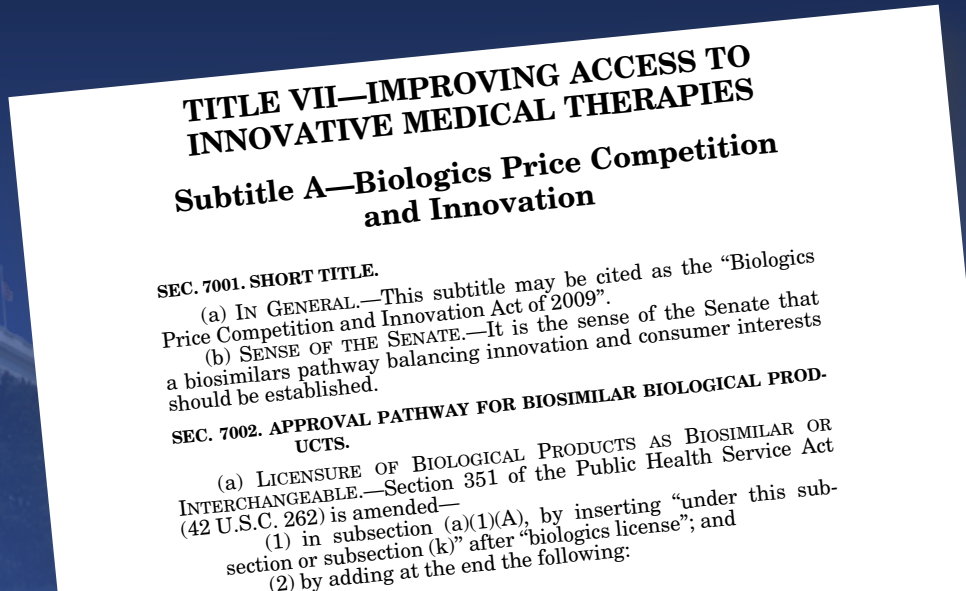
(1) in subsection (a)(1)(A), by inserting "under this subsection or subsection (k)" after "biologics license"; and

(2) by adding at the end the following:

What Does the Law Say About Interchangeability and Substitution?

Biologics Price Competition and Innovation Act, Section (351)(i)(3)

"(3) The term 'interchangeable' or 'interchangeability,' in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the **biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.**



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FDA Guidance

FDA Guidance 2012-2013

2012:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.
- Quality Considerations in Demonstrating Biosimilarity to a Reference Product Protein.
- Biosimilars: Questions and Answers Regarding BPCIA.

2013:

- Formal Meetings between FDA and Biosimilar Biologic Product Sponsors or Applicants.
- Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Availability.

February 27, 2012: ASBM Hosts Capitol Hill Biosimilars Forum

On February 27, 2012, the Alliance for Safe Biologic Medicines and Bloomberg Government hosted a **Biosimilars Forum** on Capitol Hill to discuss the FDA's draft guidance documents on biosimilar product development.

Panelists included:

- Brian Rye, Health Care Financial Analyst with Bloomberg Government
- Dr. Richard Dolinar, Chairman of the Alliance for Safe Biologic Medicines
- Dr. David Charles, Chief Medical Officer, Vanderbilt Neuroscience Institute, Chairman of the Alliance for Patient Access, and ASBM member partner
- Seth Ginsberg, Co-Founder and President of the Global Health Living Foundation, and ASBM member partner
- Andrew Spiegel, CEO and Co-Founder of the Colon Cancer Alliance, and ASBM member partner
- Martha Raymond, Patient Advocate, Colon Cancer Alliance
- Jeffrey P. Kushan, Partner, Sidley-Austin LLP

April 16, 2012:
ASBM Submits Comments to FDA on its Draft Guidance

"We are pleased with the FDA biosimilar draft guidance but it leaves a lot of questions unanswered—particularly when it comes to the requirement of clinical studies and pharmacovigilance.

There can be no grey area when it comes to patient safety. Unwanted immunogenicity is the preeminent safety challenge associated with biological therapeutics and can result in unexpected or sometimes severe adverse effects."

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ALLIANCE for SAFE BIOLOGIC MEDICINES

April 16, 2012

The Honorable Margaret Hamburg
Commissioner
Food and Drug Administration (FDA)
Division of Dockets Management (HFA—305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Docket Number FDA–2011–D–0605); Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Docket Number FDA-2011-D-0602); Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Docket Number FDA-2011-D-0611)

Dear Commissioner Hamburg:

Thank you for the opportunity to comment on the recently released biosimilar draft guidance documents. The Alliance for Safe Biologic Medicines (ASBM) is keenly interested in working with the U.S. Food and Drug Administration (FDA) to carve a biosimilars pathway that balances patient safety with the intentions of the Patient Protection and Affordable Care Act (PPACA) to foster price competition and reduce costs.

Recognizing it is an immense task to formalize the regulatory pathway for biosimilars, we appreciate your ongoing efforts to consult with stakeholders. We also look forward to continuing collaboration with the FDA on steps to prioritize patient safety as biosimilars are made available to patients in the United States.

ASBM believes patient safety must be the non-negotiable priority in developing a framework for the approval of biosimilar medicines. Unlike traditional pharmaceutical drugs that are made from well characterized, most biologics are developed from [illegible] that are not easily replicated.

May 11, 2012:
ASBM and Its Members Testify at FDA Hearing

- ASBM Chairman Richard Dolinar, MD testified.

- Of the 33 organizations that testified throughout the day, 10 were ASBM members.

- ASBM represented six of the eight patient groups that spoke during the day.

ASBM members who testified included:

- Alliance for Patient Access
- Colon Cancer Alliance
- Global Healthy Living Foundation
- RetireSafe
- HealthHIV
- National Alliance on Mental Illness
- Amgen, Inc.
- Biotechnology Industry Organization
- Genentech, Inc.

August 2012: ASBM Letter to FDA on Biosimilar Naming

FDA Commissioner Margaret Hamburg

"We commend the FDA for its longstanding commitment to patient safety and we believe that instituting a system of unique names for biologic medicines will achieve the common goal of enhancing access to life-changing therapies while also protecting the safety of patients we represent."

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ALLIANCE for SAFE BIOLOGIC MEDICINES

August 30, 2012

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg,

We appreciate the opportunities that the Food and Drug Administration (FDA) has given stakeholders to provide input as the FDA develops guidance and policies on biosimilars. The Alliance for Safe Biologic Medicines (ASBM), has been working for nearly two years to support the FDA in its mission to safely bring biosimilars to patients in the U.S. In just the past few months, we submitted comments on the draft biosimilar guidance, testified at the May 11 Public Hearing and are working with our National Advisory Board to develop a position on physician notification. In September, we will begin hosting roundtable discussions across the country with physicians, patients and pharmacists on notification and on naming. At two panels ASBM, I will be presenting at two panels on notification and on naming.

FDA Guidance Slow in Coming

- Six years since the Biologics Price Competition and Innovation Act of 2009 (BPCIA).
- No guidance yet on naming and/or interchangeability.
- 2014: Rep. Anna Eshoo (D-Calif. 18th Cong. Dist.) has sent a letter to FDA asking for a timeline on issuance and finalization of these guidances.

Scheduled FDA Guidance for 2015:

- Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCIA)
- Considerations in Demonstrating Interchangeability to a Reference Product
- Labeling for Biosimilar Biological Products
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity
- Naming?

FDA April 28th Guidance

- The U.S. is still in the process of developing its Biosimilar Approval Pathway.
- Nearly identical to February 2012 guidance.
- FDA will use totality of evidence submitted.
- No clinically meaningful differences in terms of safety, purity, and potency.

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Monday, May 04, 2015

FDA WEEK - 05/01/2015

FDA Lays Out Case-By-Case Scientific Approach To Prove Biosimilarity

Posted: April 30, 2015

FDA issued final guidance Tuesday (April 28) describing a case-by-case approach for demonstrating biosimilarity to a reference product. The agency says in the final guidance -- which is essentially identical to draft guidance issued in February 2012 -- that biosimilar sponsors should use a stepwise approach in close consultation with FDA to develop the evidence needed as the agency will consider the totality of evidence on a case-by case basis in evaluating a sponsor's evidence. The results of some tests and studies may preclude the need for other steps in the process or signal the way the next step is specifically designed, the agency says.

The agency says a biosimilar sponsor should begin with a structural analyses, followed by functional assays, then animal data and then possible clinical studies and postmarket safety monitoring considerations. Again FDA stresses that biosimilar companies should work in consultation with FDA to determine which data is necessary depending on the results of particular studies.

FDA April 28th Guidance, Continued

- Biosimilar sponsors should conduct animal studies.
- Clinical studies when needed.
- Robust post-marketing safety monitoring.
- Key issues remaining to be clarified:
  - Naming
  - Labeling

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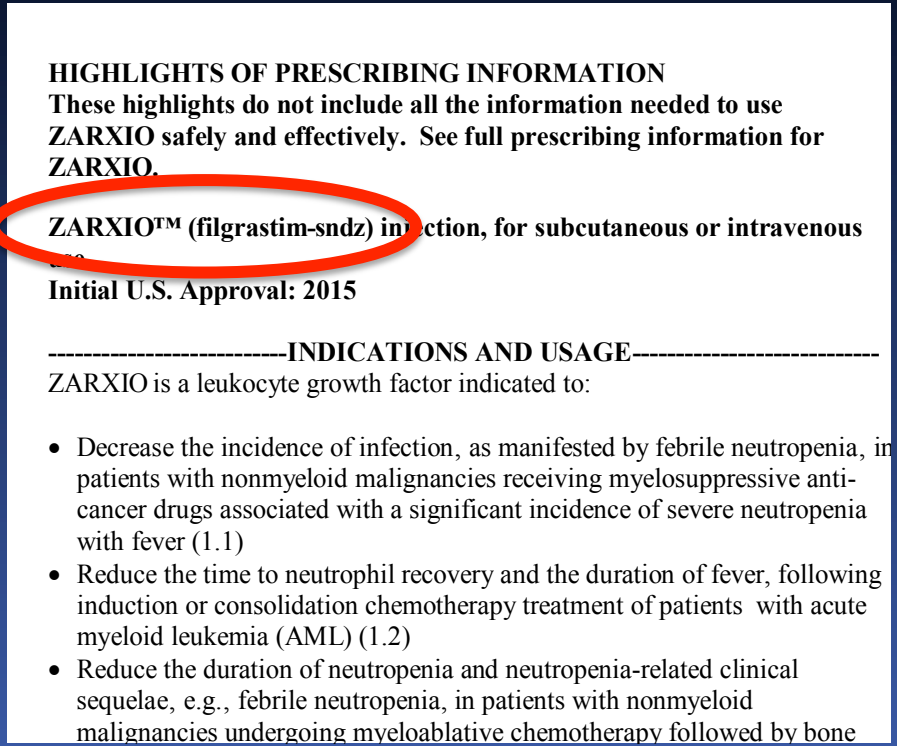
Biosimilar Naming

First U.S. Biosimilar has a Distinguishable Name.

- Zarxio (filgrastim-sndz).
- Uses DIFFERENTIATING SUFFIX similar to the WHO's own Biological Qualifier (BQ) proposal.
- Suffix tied to name of manufacturer (entity responsible for safety and efficacy of product).
- FDA has not yet indicated official support for or against distinguishable naming.



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Benefits of Distinguishable Naming:

CLEAR PRODUCT IDENTIFICATION
Distinguishable names facilitate CLEAR COMMUNICATION between physician, patient and pharmacist.

- Biosimilars **must** be distinguishable both from their reference product and from other approved biosimilars referencing the same originator product.

CLEAR PRESCRIBING & DISPENSING
Biosimilars are not interchangeable with the reference product and clear product identification will help prevent inadvertent and inappropriate substitution.

Benefits of Distinguishable Naming, Continued:

ACCURATE TRACKING

Distinguishable names ensure proper attribution of adverse events and aid in long term tracking of safety and efficacy.

MANUFACTURER ACCOUNTABILITY

Manufacturers should be held accountable for the long-term safety and efficacy of their products—differentiating suffixes tied to manufacturer or marketing authorization holder will accomplish this.

August 2014: ASBM and 70+ Patient Groups Write FDA in Support of Distinguishable Naming

The Alliance for Safe Biologic Medicines (ASBM), along with dozens of patient organizations, write Commissioner Hamburg to encourage the FDA to adopt a policy of **distinguishable nonproprietary names for biosimilars** and to issue guidance reflecting distinguishable naming as a priority for the well-being of patients.

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ALLIANCE for SAFE BIOLOGIC MEDICINES

August 14, 2014

The Honorable Margaret Hamburg
Commissioner
Food and Drug Administration (FDA)
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

On behalf of the Alliance for Safe Biologic Medicines (ASBM) and the dozens of patient organizations listed below, **we are writing to encourage the FDA to adopt a policy of distinguishable nonproprietary names for biosimilars, and to issue guidance reflecting distinguishable naming as a priority for the well-being of patients.**

In light of the recent announcement that the FDA has accepted the first application for a

May 7, 2015: Senators Write FDA on Biosimilar Naming

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FDAnews Drug Daily Bulletin
Pharmaceuticals / Regulatory Affairs / Submissions and Approvals

GOP Senators Request FDA Clarification of Biosimilars Policy

May 7, 2015

Republicans on the Senate HELP Committee are taking the FDA to task for failing to shore up policies on biosimilar naming and interchangeability before approving the first biosimilar drug nearly two months ago.

Sandoz made history in March when the FDA approved Zarxio (filgrastim-sndz), a biosimilar version of Amgen's Neupogen (filgrastim) chemotherapy drug. Though the drug has a unique name, the FDA made clear at the time that the name was just a placeholder and that it would decide later whether biosimilars should get unique names or use international nonproprietary names.

In a letter to Acting FDA Commissioner Stephen Ostroff, HELP Chairman Lamar Alexander (R-Tenn.) and seven other senators expressed confusion about what a placeholder name is and asked the agency to explain what kind of legal authority it has to issue that name and/or change it later.

The senators also want the FDA to explain exactly how it
placeholder name and how the agency
patients and

May 19, 2015: ASBM Meets with Administration Officials on Naming

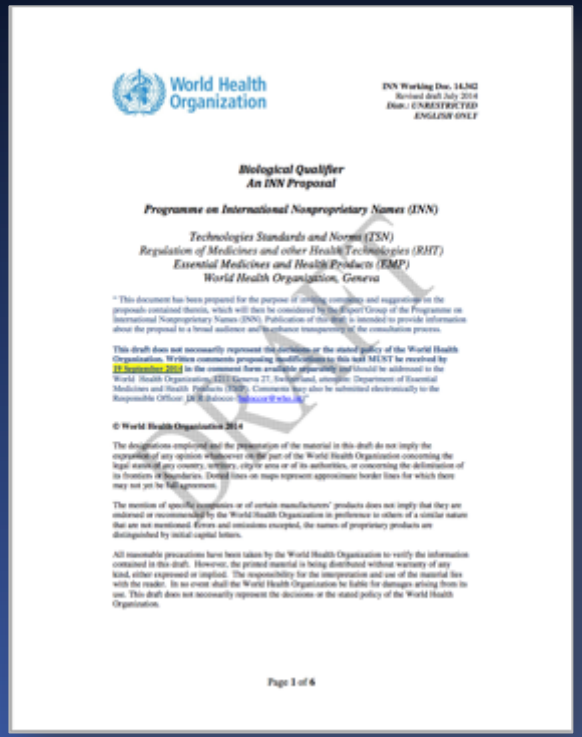
Dr. Gewanter and Mr. Reilly met with Executive Branch officials to discuss the need for distinguishable naming.

In attendance were officials from:

- Office of Management and Budget (OMB)
- Office of Information and Regulatory Affairs (OIRA)
- The National Economic Council (NEC)
- Department of Health and Human Services (HHS)

Distinguishable Naming: WHO Proposal

- The WHO has proposed adding a unique, random 4-letter code called a Biological Qualifier (BQ) to the INN of all biologics, including biosimilars, to differentiate them.
- Adherence to the BQ System is voluntary. A similar system is already in place in Japan. FDA has not yet weighed in.
- ASBM chairman Dr. Harry Gewanter and its Advisory Board Chair, pharmacy professor Dr. Philip Schneider, participated this month a meeting of the WHO's Consultation on International Nonproprietary Names and are doing so again in June.



World Health Organization

INN Working Doc. 14.302
Revised draft July 2014
Distr.: UNRESTRICTED
ENGLISH ONLY

Biological Qualifier
An INN Proposal

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms (TSN)
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

* This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Group of the Programme on International Nonproprietary Names (INN). Publication of this draft is intended to provide information about the proposal to a broad audience and to enhance transparency of the consultation process.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization. Written comments proposing modifications to this text MUST be received by 19 September 2014 in the comment form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr R Johnson: johnsonr@who.int.

DRAFT

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Examples of Potential Areas For Creation of Global Standards

Approval Processes:
Should biosimilars have to undergo rigorous clinical trials, to collect data that ensures patient safety and promotes physician confidence?

Biosimilar Naming:
Unique names for a biosimilar provide more information to the physician, and helps track and trace adverse effects.

Biosimilar Substitution:
When can a biosimilar be substituted for a reference biologic medicine, and by whom?


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Thank You For Your Attention