

# [L7] A Biosimilars Update: Regulation and Legislation

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## Learning Objectives

- Explain common and unique features of biosimilars state legislation and review the status of biosimilar substitution laws.
- Discuss FDA 2017 regulatory updates for biosimilars and anticipated changes for 2018.
- Evaluate biosimilar uptake and extrapolate how current and future biosimilars laws will affect uptake.

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## Financial Relationship Disclosures

- Reginia Benjamin, BS, JD reports having no financial relationships with any commercial interests during the past 12 months.
- Edward Li, PharmD, MPH, BCOP is a consultant for New Century Health, on the speaker board for Pfizer, and on the advisory board for Eli Lilly and Company, Heron Therapeutics, Mylan, and Taiho.

This slide deck has been peer reviewed to mitigate promotional bias.

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**#amcp2018**

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**MARCH 2010**

**It is the sense of the United States Senate that a biosimilars pathway balancing innovation and consumer interests should be established.**

Biologics Price Competition and Innovation Act.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm216146.pdf>

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## **Biologics Price Competition and Innovation Act (BPCIA) of 2009 – signed March 2010**

42 U.S.C. 262 (i)(2) The term ‘biosimilar’ or ‘biosimilarity’ in reference to a biological product that is the subject of an application under subsection (k) means –

- (A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- (B) 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.

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## BPCIA

42 U.S.C. 262 (i) (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.

## BPCIA

42 U.S.C. (k)(4) Safety standards for determining interchangeability. Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application is sufficient to show that –

- (A) the biological product –
  - (i) is biosimilar to the reference product; and
  - (ii) can be expected to produce the same clinical result as the reference product in any given patient; and

## BPCIA

(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between 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

## Purple Book

**Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations**  
First edition released September 9, 2014

In addition to the date licensed, also includes whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product).

## Purple Book

Healthcare providers can prescribe biosimilar and interchangeable biological products just as they would prescribe other medications.

The BPCI Act describes an interchangeable product as a product that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

In contrast, FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level.

## Orange Book

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE  
EVALUATIONS

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER  
SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND  
DRUG ADMINISTRATION

38th EDITION 2018



## Federal Legislation

### “Creating and Restoring Equal Access to Equivalent Samples Act”

- S. 974 – Sen. Patrick Leahy (D-VT)
- H.R. 2212 – Rep. Tom Marino (R-PA)
- To create competition in the market for biological products by facilitating the entry of lower-cost generic and biosimilar versions
- Contains provisions for drugs and biological products that are subject to REMS program

## CREATES ACT

- To help developers of generic drugs and biosimilar biological products obtain quantities of the reference drug or biological product to support their application
- Creates a civil cause of action for failure to provide sufficient quantities of a covered product
- Director of the FDA Center for Drug Evaluation and Research has testified that some manufacturers have used REMS and internal distribution restrictions as a reason not to sell to generic product developers

# FAST ACT

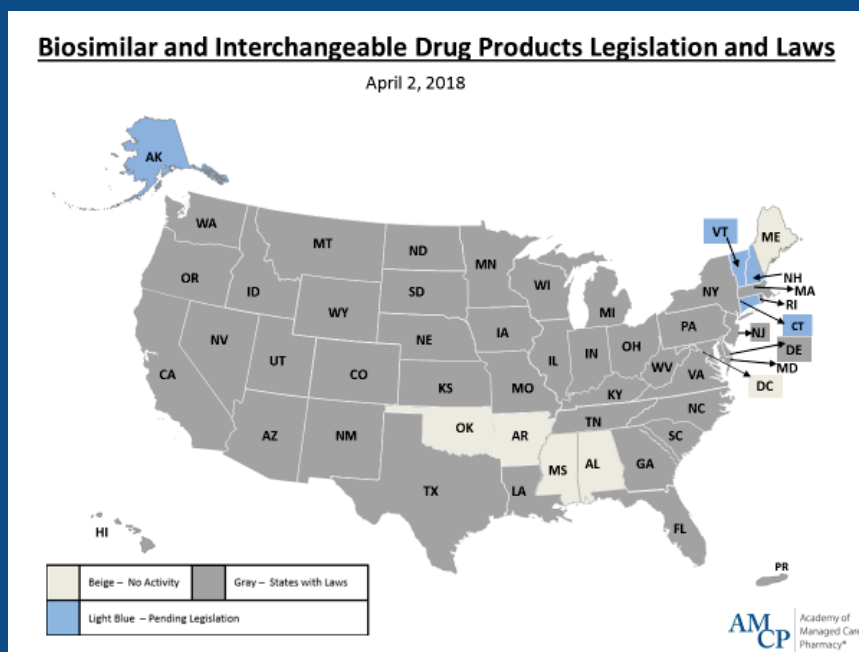
- Fair Access for Safe and Timely Generics (FAST) Act
  - H.R. 2051 – Rep. David B. McKinley (R-WV)
- Not a companion to CREATES, but both designed to address the same issues
- Designed to ensure that eligible product developers have competitive access to approved drugs and licensed biological products, so as to enable eligible product developers to develop and test new products
- FAST focuses on a regulatory solution, whereas CREATES focuses on a judicial solution

# Biosimilars State Law Landscape

# State Landscape Today and Looking Ahead to 2019

- 41 States and Puerto Rico with Laws
- 4 States still pending in 2018 – AK, CT, NH, and VT
- 5 States with no laws and not pending in 2018 – AL, AR, ME, MS, and OK
- Anticipate legislation in 2019 for Arkansas and Maine

## State Laws and Pending Legislation 2018



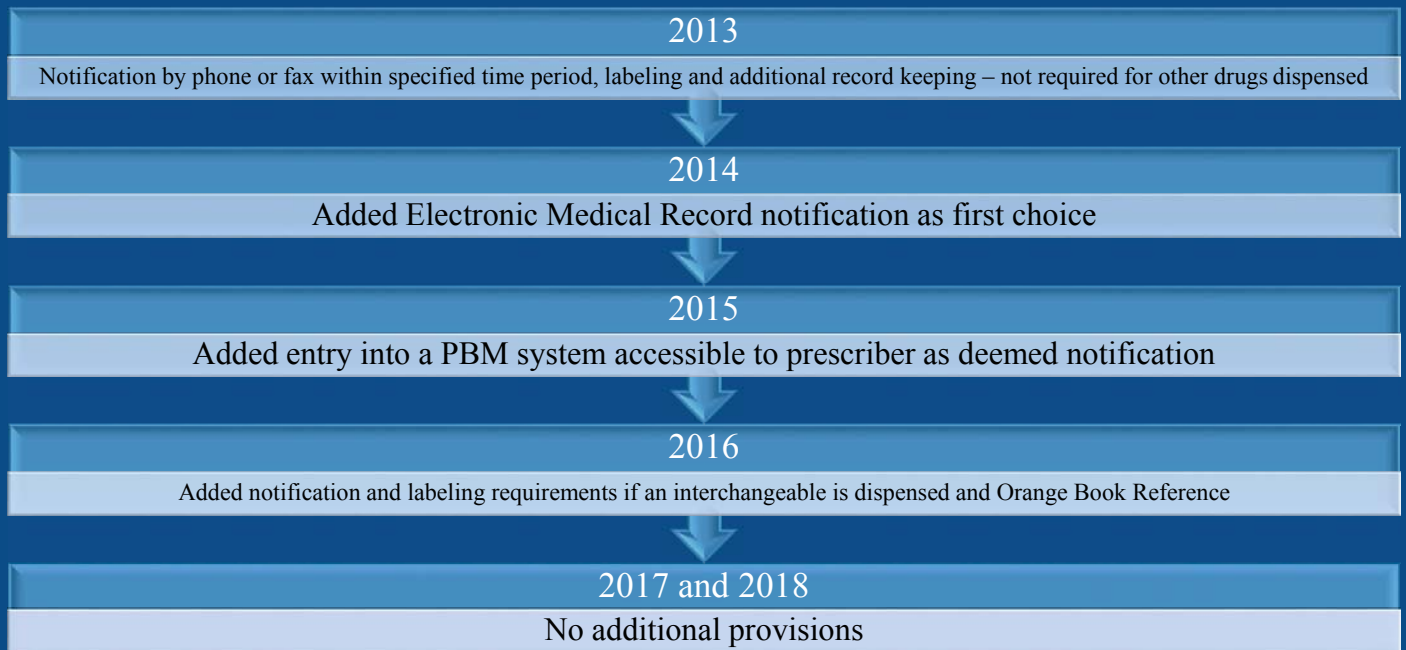
State Biosimilar Tracking Chart

# State Laws Enacted Concerning Biosimilars and/or Interchangeables

2013	2014	2015	2016	2017	2018	Pending
Florida North Dakota Oregon Utah Virginia	Delaware Indiana Massachusetts	California Colorado Georgia Illinois Louisiana New Jersey North Carolina Tennessee Texas Utah* Washington	Arizona Hawaii Idaho Kentucky Missouri Ohio Oregon* Pennsylvania Rhode Island	Iowa Kansas Maryland Montana Nebraska Nevada New Mexico New York South Carolina	Michigan South Dakota West Virginia Wisconsin Wyoming	Alaska Connecticut New Hampshire Vermont

\* = Amended law

## Overview of State Legislative Activity



# Overview of State Definitions of Interchangeable

States do not use the FDA definition of interchangeable instead they refer to the section (k) language which references standards of interchangeability

States are making the definition of interchangeable a two part definition:

- (1) a biological product determined by the FDA to meet the standards of interchangeability set forth in section (k)
- (2) a biological product determined by the FDA to be therapeutically equivalent as set forth in the Orange Book

## Additional State Legislative Language

- Notice to the patient required prior to dispensing
- Timeframe for notice varies from within 24 hours up to 5 days
- Additional labeling requirements and record retention timeframes
- Approval by the patient required prior to dispensing
- State Board of Pharmacy must maintain information on its website of FDA approved interchangeable biosimilars
- A pharmacist who selects an equivalent drug product or interchangeable biological product assumes no greater liability for selecting the dispensed drug or biological product than would be incurred in filling a prescription for a drug or biological product prescribed by its established, generic, or proper name.

## North Dakota: Title 19 Section 19-02.1-14.3 (2013)

A pharmacy may substitute a prescription biosimilar product for a prescribed product **only if**:

- a. The biosimilar product has been determined by the United States Food and Drug Administration to be **interchangeable** with the prescribed product;
- b. The prescribing practitioner does not specifically indicate in the practitioner's own handwriting "brand medically necessary" on a written prescription, does not expressly indicate that an oral prescription is to be dispensed as communicated, or has not taken a specific overt action to include the "brand medically necessary" language with an electronically transmitted prescription;
- c. The pharmacist informs the individual receiving the biological product that the biological product may be substituted with a biosimilar product and that the individual has a right to refuse the biosimilar product selected by the pharmacist and the individual chooses not to refuse;
- d. **The pharmacist notifies the prescribing practitioner orally, in writing, or by electronic transmission within twenty-four hours of the substitution; and**
- e. **The pharmacy and the prescribing practitioner retain a record of the interchangeable biosimilar substitution for a period of no less than five years.**

## Delaware: Title 24 Section 2549A (2014)

A pharmacist may substitute for a prescribed biological product only if:

- (1) The practitioner has not expressly prohibited substitution in a manner specified in § 2549 of this title;
- (2) The product to be substituted has been designated by the Federal Food and Drug Administration as interchangeable with or therapeutically equivalent to the prescribed product;
- (3) **The pharmacist informs the patient or the patient's adult representative that an interchangeable biological product has been dispensed; and**
- (4) **The pharmacist indicates on the prescription and on the prescription label the name of the manufacturer of the interchangeable biological product substituted unless the practitioner indicates otherwise.**

## Delaware: Title 24 Section 2549A (2014)

b) If a biological product is dispensed, the pharmacist or the pharmacist's designee shall, within a reasonable time but not to exceed 10 days following dispensing, communicate to the practitioner the name and manufacturer of the biological product dispensed, by: (1) Recording such information in an interoperable electronic health records system shared with the prescribing practitioner, to the extent such a system is in place between a pharmacist and practitioner; or (2) In the case where electronic health records are not in place between a pharmacist and a practitioner, communicating such information to the practitioner using any prevailing means available. No communication is required under this subsection where there is no interchangeable or therapeutically equivalent biological product for the prescribed biological product, or where a refill prescription is not changed from the biological product originally dispensed. (c) The pharmacy shall maintain a record of the biological product dispensed as required in § 2532 of this title. (d) The Board of Pharmacy shall maintain a link on its web site to the current list of all biological products determined by the Federal Food and Drug Administration to be interchangeable with a specific biological product.

## California: Chapter 9 Article 4 (2015)

(a) A pharmacist filling a prescription order for a prescribed biological product may select an alternative biological product only if all of the following:

- (1) The alternative biological product is **interchangeable**.
- (2) The prescriber does not personally indicate "Do not substitute," or words of similar meaning, in the manner provided in subdivision (d).

(b) **Within five days following the dispensing** of a biological product, a dispensing pharmacist or the pharmacists' designee shall make an entry of the specific biological product provided to the patient, including the name of the biological product and the manufacturer. The **communication shall be conveyed by making an entry that can be electronically accessed by the prescriber through one or more of the following electronic records systems:**

- (1) An interoperable electronic medical records system.
- (2) An electronic prescribing technology.
- (3) A pharmacy benefit management system.
- (4) A pharmacy record.

(c) **Entry into an electronic records system as described in subdivision (b) is presumed to provide notice to the prescriber.**

(d) If the pharmacy does not have access to one or more of the entry systems in subdivision (b), the pharmacist or the pharmacist's designee shall communicate the name of the biological product dispensed to the prescriber using facsimile, telephone, electronic transmission, or other prevailing means ...

## Arizona: Title 32 – Section 32-1963.01 Professions and Occupations (2016)

A. If a medical practitioner prescribes a brand name drug and does not indicate an intent to prevent substitution as prescribed in subsection E of this section, a pharmacist may fill the prescription with a generic equivalent drug.

B. A pharmacist may substitute a biological product for a prescribed biological product only if all of the following conditions are met:

1. The United States FDA has determined the substituted product to be an interchangeable biological product.
2. The prescribing physician does not designate in writing or electronically that substitution is prohibited in a manner pursuant to subsection E of this section.
3. The pharmacy informs the patient or person presenting the prescription of the substitution pursuant to subsection C of this section.
4. Within five business days after dispensing a biological product, the dispensing pharmacist or the pharmacist's designee makes an entry of the specific product provided to the patient, including the name of the product and the manufacturer. The communication shall be conveyed by making an entry that is electronically accessible to the prescriber through an interoperable electronic medical records system, an electronic prescribing technology, a pharmacy benefit management system, or a pharmacy record. **Entry into an electronic records system as described in this paragraph is presumed to provide notice to the prescriber.** Otherwise, the pharmacist shall communicate the biological product dispensed to the prescriber using fax, telephone, electronic transmission, or other prevailing means...

## Arizona: Title 32 – Section 32-1963.01 Professions and Occupations (2016)

5. "Interchangeable biological product" means a biological product that either:

(a) The United States food and drug administration has licensed and determined meets the safety standards for determining interchangeability pursuant to 42 United States Code section 262(k)(4).

(b) Is determined to be therapeutically equivalent as set forth in the latest edition of the supplement to the United States food and drug administration's approved drug products with therapeutic equivalence evaluations.



## Maryland Article 12-101 (2017)

(C) “biological product” has the meaning stated in 42 u.S.C. § 262.

(M) “interchangeable biological product” means a biological product that is:

- (1) licensed and determined by the united states food and drug administration to meet the standards for interchangeability under 42 u.S.C. § 262(k)(4); or
- (2) determined to be therapeutically equivalent as stated in the latest edition of or supplement to the united states food and drug administration’s approved drug products with therapeutic equivalence evaluations (the “orange book”).

## Maryland Article 12-504.1 – Health Occupations (2017)

(A) Except as provided in subsection (d) of this section, within 5 business days after dispensing a biological product to a patient, the dispensing pharmacist or the pharmacist’s designee shall communicate the specific biological product dispensed, including the name and manufacturer of the biological product, to the prescriber.

(B) Except as provided in subsection (c) of this section:

(1) The communication required under subsection (a) of this section shall be provided by making an entry that is electronically accessible to the prescriber through:

- (i) An interoperable electronic medical records system;
- (ii) An electronic prescribing technology;
- (iii) A pharmacy benefits management system; or
- (iv) A pharmacy record; and

## Maryland Article 12-504.1 – Health Occupations (2017)

(2) making an entry through a mechanism listed in paragraph (1) of this subsection is presumed to provide the communication to the prescriber required under subsection (a) of this section.

(C) if the mechanisms listed in subsection (b)(1) of this section are not available, the communication required under subsection (a) of this section may be provided by facsimile, telephone, electronic transmission, or other means.

## South Dakota Section 36-11-2 – 2018

(14) "Interchangeable biological product," a biological product that the U.S. Food and Drug Administration either has licensed and determined meets the standards for interchangeability pursuant to 42 U.S.C. 262(k)(4), as of January 1, 2018, or has determined is therapeutically equivalent as set forth in the latest edition of, or any supplement to, the Food and Drug Administration's Approved Drug Products with Therapeutic Equivalence Evaluations publication as adopted by the board pursuant to chapter 1-26

## South Dakota Section 36-11(new section) – 2018

A pharmacist dispensing a prescription drug order for a biological product prescribed by its brand or proper name may select an interchangeable biological product of the prescribed product. Within five business days following the dispensing of a biological product, the dispensing pharmacist or the pharmacist's designee shall make an entry of the specific product provided to the patient, including the name of the product and the manufacturer. The communication shall be conveyed by making an entry that is electronically accessible to the prescriber through:

- (1) An interoperable electronic medical records system;
- (2) An electronic prescribing technology;
- (3) A pharmacist benefit management system; or
- (4) A pharmacy record.

## South Dakota Section 36-11(new section) – 2018

Any entry into an electronic records system as described in section 9 of this Act is presumed to provide notice to the practitioner. Otherwise, the pharmacist shall communicate the biological product dispensed to the practitioner using facsimile, telephone, electronic transmission, or other prevailing means, if communication is not required where:

- (1) There is no interchangeable biological product approved by the U.S. Food and Drug Administration for the product prescribed;  
or
- (2) A refill prescription is not changed from the product dispensed on the prior filling of the prescription.

## Issues and Challenges with State Action

- State laws not consistent with the BPCIA intent – to support price competition and innovation in the market balanced with consumer interests
- Generally no authority for pharmacists to substitute an interchangeable for the reference product without the intervention of the health care provider
- Generally no recognition of the Purple Book as the FDA source
- States will probably continue to enact laws that are not consistent with BPCIA intent, change the BPCIA definitions and create barriers to dispensing
- Patient and prescriber confidence in these FDA approved products may be hindered by restrictive state laws
- Essential that we continue to provide patients, pharmacists, prescribers and decision makers with educational resources to better inform them of the potential for increased access to safe and more cost effective medications as more biosimilar and eventually interchangeable bio products enter the market

## Current Challenges Affecting Biosimilar Marketplace Adoption in United States

- Federal and state regulations on biosimilars confusing, incomplete, and often discourage adoption
- Nine biosimilars approved in the United States but only three marketed
  - filgrastim-sndz (Zarxio®) biosimilar to filgrastim (Neupogen®) launched in September 2015
  - infliximab-dyyb (Inflectra®) biosimilar to infliximab (Remicade®) launched November 2016
  - infliximab-abda (Renflexis®) biosimilar to infliximab (Remicade®) launched July 2017
- Patent litigation and settlement agreements delaying significant market launches until 2022-2023
  - Biosimilars to “blockbuster agents” such as adalimumab (Humira®), trastuzumab (Herceptin®), and bevacizumab (Avastin®) have been approved in the United States, but could be delayed until 2022-2023

## Why is Biosimilars Education Important?

- Education is one of the keys to successful adoption

*IMS Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets*

- “Stakeholder engagement is essential to success of the biosimilar program.”

Janet Woodcock, MD, Director of FDA’s Center for Drug Evaluation and Research before U.S. House Energy & Commerce Committee (2016)

## Why is Biosimilars Education Important?

- The Biosimilars Resource Center (BRC) provides needed educational resources and information on biosimilars to health care providers and other stakeholders in a policy-neutral and non-promotional manner.
- Biosimilars have the potential to significantly decrease health care costs in the United States and improve access to treatment for patients. The need for education of health care providers on how to prescribe and dispense cost effective biosimilars is critical to driving adoption and maximizing their use in a safe and effective manner for patients.

# Biosimilars Resource Center

The screenshot shows the Biosimilars Resource Center website. At the top, there is a navigation bar with links for 'ABOUT US', 'BIOSIMILARS FACTS', 'LAWS & REGULATIONS', and 'EDUCATION'. Below the navigation bar is a large image of a group of healthcare professionals in a meeting. To the right of the image is a headline: 'Unbiased. Factual. Up-to-Date.' followed by a paragraph: 'Announcing a new biosimilars resource for health care providers. BRC is your source for educational programs, including accredited continuing education. Click "Stay Informed" to receive updates from this site and on biosimilars.' Below this are four main content areas: 'WHAT ARE BIOSIMILARS?' with a magnifying glass icon, 'LEGISLATIVE MAP' with a map icon, 'NEWS AND PERSPECTIVES' with a megaphone icon, and 'STAY INFORMED' with an envelope icon.



[BiosimilarsResourceCenter.org](http://BiosimilarsResourceCenter.org)

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## AMCP Policy Digest – Policy 0802 Biosimilar Drug Therapies

AMCP supports:

An abbreviated licensure pathway for the approval of biosimilar biologic drug therapies. In order to strike an appropriate balance between bringing safe and effective drugs to market and maximizing patient access to affordable drugs, the FDA should determine on a case-by-case basis the need for additional clinical studies prior to approval, as well as any post-marketing studies. Manufacturers of approved biosimilars should be allowed to use the same government-approved/international non-proprietary name as the reference product. The FDA should also provide clear rules for the designation of a biosimilar product as interchangeable with a reference product, similar to the current "AB" ratings used for small-molecule chemical drugs. A designation of interchangeability should not be a requirement as a condition for approval of a biosimilar product.

(See AMCP Where We Stand Position Statement - Biosimilar Drug Therapies)

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# AMCP Policy Statements

## Policy Digest Statement – Policy 0802 – Biosimilar Drug Therapies

- <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=21736#page=28>

## Where We Stand Statement on Biosimilars Drug Therapies

- <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=20018>

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# Biosimilars FDA Regulation & Uptake

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**Portland, Maine**

## Biosimilar Regulatory Updates

- 2017 Updates
  - Interchangeability draft guidance released (Jan 2017)
  - Biosimilar User Fee Act (BsUFA) Reauthorization signed into law on August 18, 2017 (BsUFA II)
- Anticipated changes in 2018
  - FDA 2018 Strategic Policy Roadmap



## BsUFA II Changes: Target Action Date

- BsUFA I

FDA  
receives  
application

10 months

FDA acts on  
90% of  
applications

- BsUFA II

FDA  
receives  
application

60-day  
filing date

10 months

FDA acts on  
90% of  
applications

– Intended to allow for more communications across the entire application cycle

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<https://www.lexology.com/library/detail.aspx?g=326d63c9-e78e-4f16-9afb-bd8e0196d13d>

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## BsUFA II Changes: Meeting Timelines

Meeting Type	Description	Change
<b>Biosimilar Initial Advisory Meeting</b>	<ul style="list-style-type: none"> <li>Discuss feasibility of product for 351(k) application</li> <li>No substantive review of summary data or full study results</li> <li>Preliminary data for comparative analytical similarity</li> <li>Overview of product development program</li> </ul>	Decrease to 75 days (from 90 days) from receipt of meeting request
<b>Type 1</b>	<ul style="list-style-type: none"> <li>Discuss clinical holds</li> <li>Special protocol assessment meetings</li> <li>Discuss safety issue, dispute resolution</li> </ul>	
<b>Type 2</b>	<ul style="list-style-type: none"> <li>Discuss proposed study design or endpoints</li> <li>FDA to provide targeted advice</li> <li>Can include substantive review of summary data</li> </ul>	Increase to 90 day (from 75 days) from receipt of meeting request
<b>Type 3</b>	<ul style="list-style-type: none"> <li>In-depth data review and advice meeting (full study reports)</li> <li>FDA provides advice regarding need for additional studies</li> </ul>	
<b>Type 4</b>	<ul style="list-style-type: none"> <li>Discuss format and content of product application</li> <li>No substantive review of data</li> </ul>	

<https://www.fda.gov/downloads/drugs/guidances/ucm345649.pdf>

<https://www.lexology.com/library/detail.aspx?g=326d63c9-e78e-4f16-9afb-bd8e0196d13d>

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## Guidance Documents

- Guidances to draft:
  - Processes and Further Considerations Related to Post-Approval Manufacturing Changes for Biosimilar Biological Product
- Guidances to update or finalize:
  - Best Practices for Communication Between IND Sponsors and FDA During Drug Development
  - Statistical Approaches to Evaluate Analytical Similarity
  - Labeling for Biosimilar Biological Products

<https://www.lexology.com/library/detail.aspx?g=326d63c9-e78e-4f16-9afb-bd8e0196d13d>

## BsUFA II Changes: Fee Increases

- Previous workload analyses have indicated the FDA is short-staffed
  - Missed metrics
  - Policy development
- BsUFA II establishes an independent fee structure for biosimilars
- Fees would increase from \$22 million in 2017 to \$87 million in 2018

<https://www.lexology.com/library/detail.aspx?g=326d63c9-e78e-4f16-9afb-bd8e0196d13d>

# Anticipated Changes in 2018

- FDA's 2018 Strategic Policy Roadmap
  1. Reduce the burden of addiction crises that are threatening American families
  2. Leverage innovation and competition to improve healthcare, broaden access, and advance public health goals
  3. Empower consumers to make better and more informed decisions about their diets and health; and expand the opportunities to use nutrition to reduce morbidity and mortality from disease
  4. Strengthen FDA's scientific workforce and its tools for efficient risk management

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM592001.pdf>

## FDA's 2018 Strategic Policy Roadmap

2. Leverage innovation and competition to improve healthcare, broaden access, and advance public health goals
  - Formation of a Biosimilar Innovation Plan (BIP)
    - More efficient development and approval process
    - “Better incentives for the adoption of safe, effective, and high-quality biosimilar drugs”
  - Issue final guidance on communication to payers about economic consequences of products which may promote value-based contracting

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM592001.pdf>

# Biosimilar Experience: Filgrastim Case Study

- Biosimilar filgrastim has been available in EU since 2008 and the US since 2015
- Recently Published reports:

Reference	Description	Population and Data Source
Marcianò I, et al. <i>BioDrugs</i> . 2016;30(4):295-306.	Retrospective cohort; descriptive analysis of drug utilization (pharmacoepi)	23 health centers in Spain; health records
Douglas AG, et al. <i>J Manag Care Spec Pharm</i> . 2017;23(12):1221-1226.	Retrospective cohort; comparative effectiveness	Humana patients enrolled in Medicare Advantage Rx Drug plan; claims data
Puértolas I, et al. <i>Eur J Clin Pharmacol</i> . 2018;74(3):315-321	Retrospective, observational; descriptive analysis of prescribing patterns and effectiveness	Administrative claims for multiple health systems in Italy

Caselli D, et al. *Biologics*. 2016; 10: 17–22.

# Descriptive Analysis of GCSF Prescribing from Five Italian Centers 2009-2014

- Retrospective, observational, multi-database drug utilization study
- Five large health centers in Italy, comprising almost 8 million people (~10% of the Italian population)
- Identified 29,083 naïve users of GCSF
- Utilization grouped by type of product:
  - Reference filgrastim
  - Biosimilar filgrastim
  - Pegfilgrastim
  - Lenagrastim

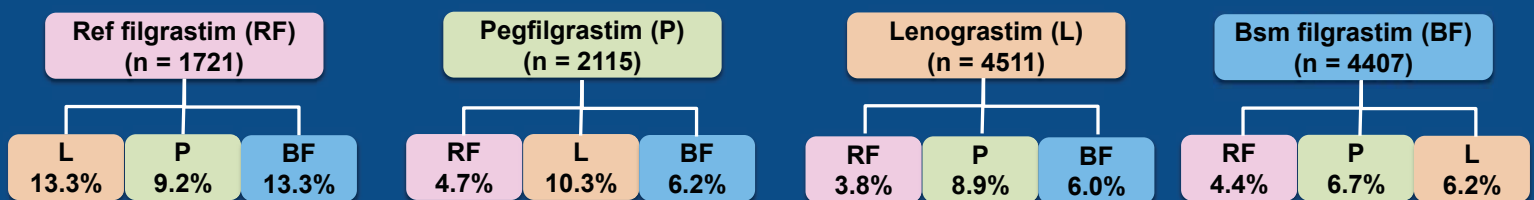
Marcianò I, et al. *BioDrugs*. 2016;30(4):295-306.

# Descriptive Analysis of GCSF Prescribing from Five Italian Centers 2009-2014

- Overall prevalence of GCSF use (per 1000) increased

2009		2014	
Overall:	0.8	Overall:	1.1
Ref filgrastim:	0.2	Ref filgrastim:	0.1
Biosim filgrastim:	--	Biosim filgrastim:	0.7
Lenagrastim:	0.5	Lenagrastim:	0.1
Pegfilgrastim:	0.1	Pegfilgrastim:	0.2

- Switching across all products occurred frequently



Marciànò I, et al. *BioDrugs*. 2016;30(4):295-306.

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## Comparative Effectiveness of Reference vs. Biosimilar GCSF for CIN

- Retrospective cohort study using administrative claims from the Humana Research Database; included patients enrolled in Medicare Advantage Prescription Drug Plan
- Oct 2015 to Sep 2016
- Patient numbers: 88 filgrastim (reference) and 101 filgrastim-sndz
- Measured incidence of FN and serious adverse drug events

Douglas AG, et al. *J Manag Care Spec Pharm*. 2017;23(12):1221-1226.

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## Comparative Effectiveness of Reference vs. Biosimilar GCSF for CIN

Measure	Filgrastim % (90% CI)	Filgrastim-sndz % (90% CI)	Incidence difference % (90% CI)	P-value
Infection and/or neutropenia	3.4 (0.9-8.6)	4.0 (1.4-8.8)	-0.6 (-5.1-4.0)	0.84
Infection and neutropenia	1.14 (0.1-5.3)	1.98 (0.4-6.1)	-0.84 (-3.8-2.1)	0.64
Adverse drug event	3.4 (0.9-8.6)	5.9 (2.6-11.4)	-2.5 (-7.5-2.5)	0.42

Douglas AG, et al. *J Manag Care Spec Pharm.* 2017;23(12):1221-1226.

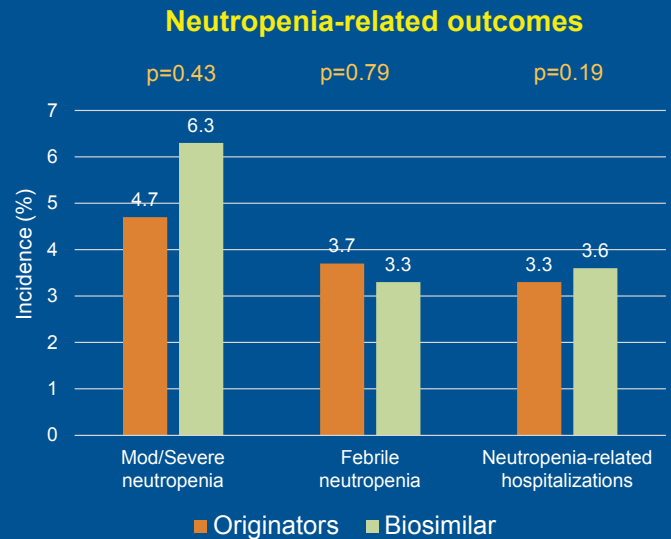
## Descriptive Analysis and Effectiveness of GCSF Products in Spain

- Retrospective cohort study of EHR data from 23 healthcare centers
- Adult patients with breast cancer who received FN primary prophylaxis during TAC regimen as adjuvant/neoadjuvant treatment
- Jan 2012 to Dec 2014
- Lenograstim, pegfilgrastim, biosimilar filgrastim
- Total of 518 TAC cycles among 98 patients

Puértolas I, et al. *Eur J Clin Pharmacol.* 2018;74(3):315-321

# Descriptive Analysis and Effectiveness of GCSF Products in Spain

	Pegfilgrastim	Lenograstim	Biosim Filgrastim
<b>Total # of TAC cycles (%)</b>	180 (34.7%)	35 (6.8%)	303 (58.5%)
<b>Dosage (mcg/kg/day), mean (SD)</b>	6 mg fixed dose	5.7 (0.9)	4.9 (0.8) p<0.001
<b>Duration (days) of GCSF per cycle, mean (SD)</b>	N/A	7.1 (1.9)	5.6 (1.4) p<0.001



Puértolas I, et al. *Eur J Clin Pharmacol.* 2018;74(3):315-321

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## Impact of Biosimilar Competition in Europe

- Descriptive analysis of price, volume, and market share of biological products after the introduction of biosimilars in Europe
- Report requested by European Commission services
- Prepared by QuintilesIMS with contributions from EFPIA, Medicines for Europe, and EuropaBio
- Four key observations
  1. Price competition
  2. Lowering the price of the reference
  3. First to market advantage
  4. Impact on patient access to biologics

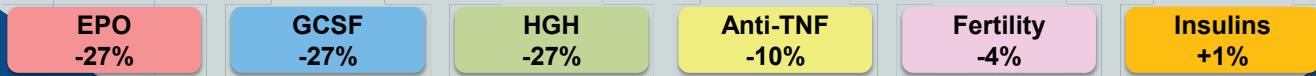
[http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017\\_V9.pdf](http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf)

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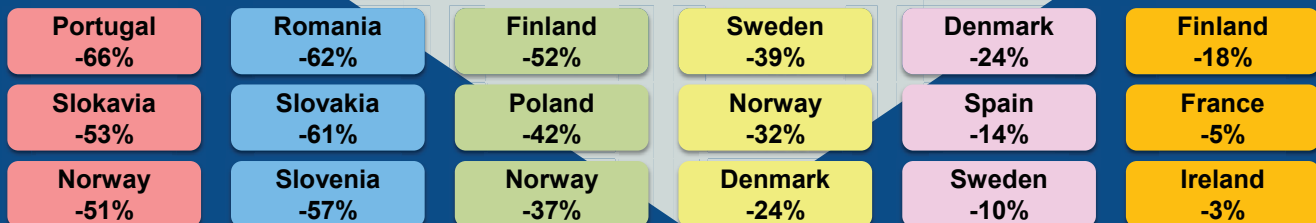
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# Key Observation #1: Price Competition

## A. Competition drives down price for the total market



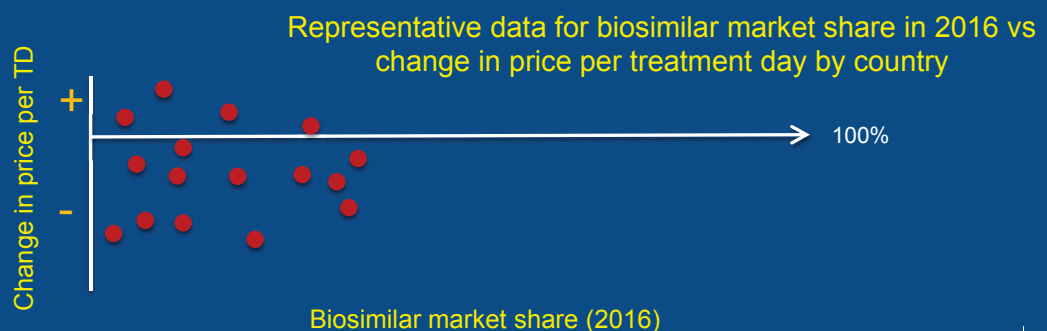
(price per treatment day in 2016 vs year before biosimilar entry)



# Key Observation #1: Price Competition

## B. Correlation between biosimilar market share and price is weak

- High savings can be seen even if biosimilar market share is low
- Price reductions can be achieved through price regulation
- Biosimilars increase competition and lower price across the whole market, even if it is not used



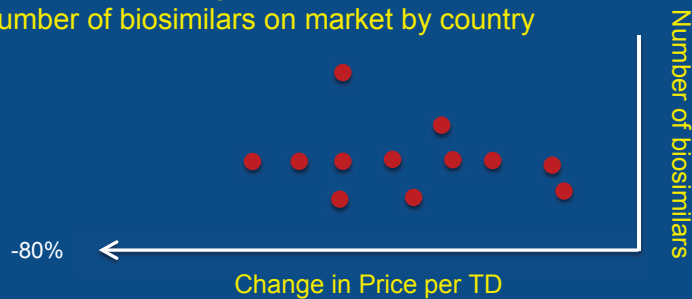


# Key Observation #1: Price Competition

## C. One biosimilar entering the market can lower prices

- Weak correlation between the number of biosimilars and change in price of total market
- Long term health of the market and to achieve full effect of competition may require multiple biosimilars

Representative data for change in price per TD compared to total number of biosimilars on market by country

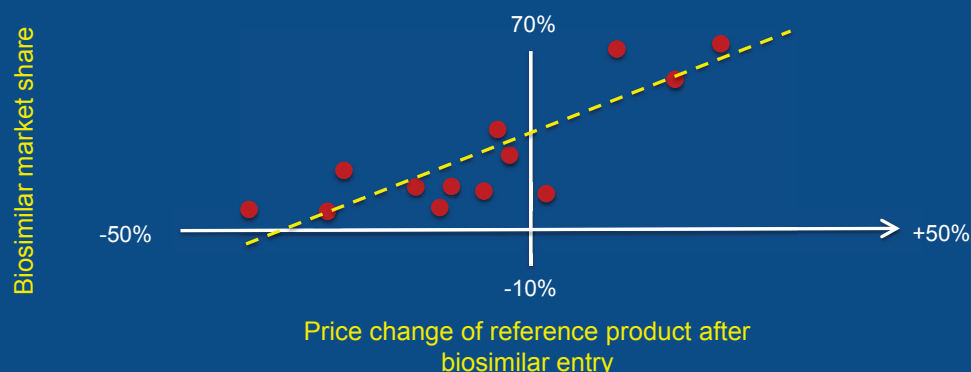


[http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017\\_V9.pdf](http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf)

# Key Observation #2: Lowering Price of the Reference

- Lowering the price of the reference can limit biosimilar market share with some therapeutics classes (anti-TNF, HGH)

Representative data for change in price of reference product vs. biosimilar market share in 2016



[http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017\\_V9.pdf](http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf)

# Key Observation #3: First to Market Advantage

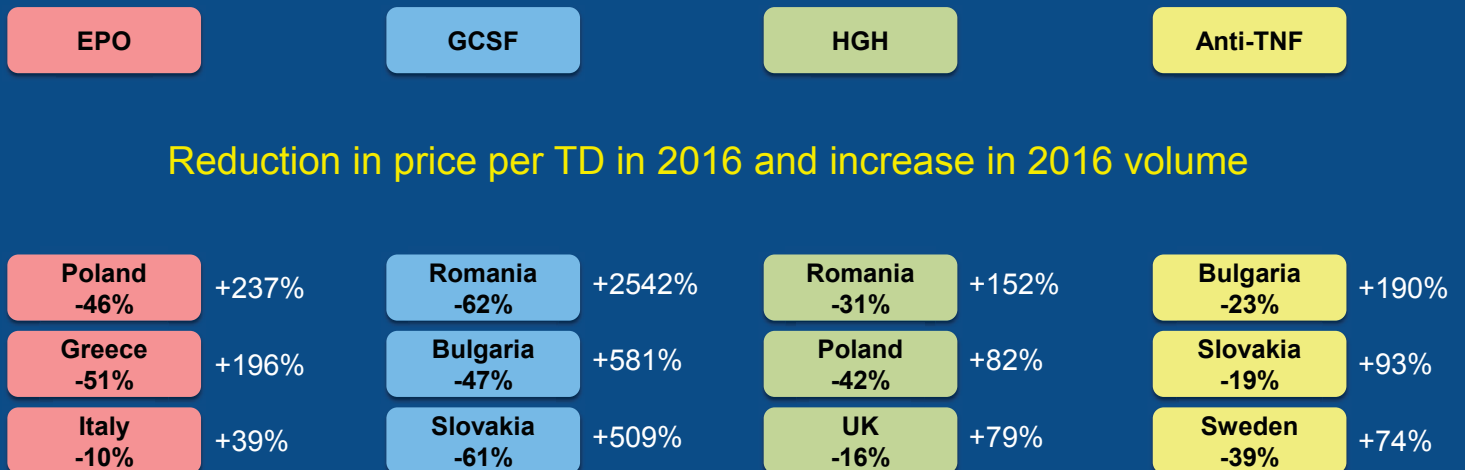
- There is a first to market advantage for biosimilars

Biosimilar market entry rank	2016 Market share across all countries: Anti-TNF	2016 Market share across all countries: EPO
1 <sup>st</sup>	72%	73%
2 <sup>nd</sup>	30%	40%
3 <sup>rd</sup>	5%	22%
4 <sup>th</sup>	0%	--

[http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017\\_V9.pdf](http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf)

# Key Observation #4: Patient Access

## A. Lower prices can increase patient access



[http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017\\_V9.pdf](http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf)

## Key Observation #4: Patient Access

### B. Overall, biosimilar competition contributes to increased patient access of the whole market

Growth in Volume per TD  
(2016 vs. year before biosimilar entry)

	Reference product only	Biosimilar and reference	Biosimilar accessible market	Total markets
GCSF	-74%	122%	63%	58%
HGH	-14%	41%	45%	45%
Anti-TNF	-10%	19%	19%	26%
Fertility	2%	16%	8%	10%
EPO	-37%	66%	4%	7%
Insulins	14%	19%	15%	4%

## Policies Driving Biosimilar Utilization: Europe

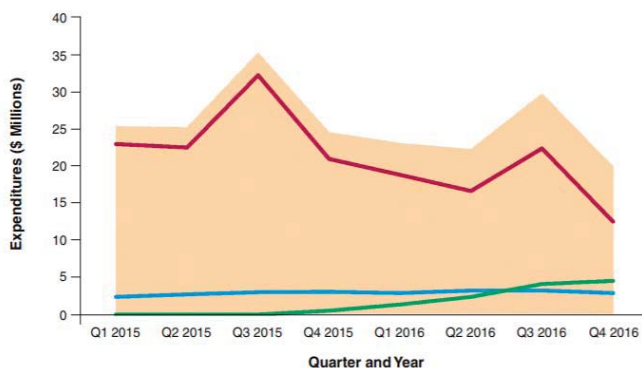
- Supply-side vs. Demand-side
- Availability
  - Approved by EMA
  - Hospitals vs. ambulatory care: restrictions vary depending on formulary
- Pricing policies
  - Regulated by national authorities for ambulatory patients
  - Percentage of reference and use of max price
- Reimbursement policies
  - Usually reimbursed for indications for which they are licensed
- Demand-side policies
  - Incentives targeting physicians to prescribe biosimilars
  - May be incorporated into pricing and reimbursement
- Pharmacist substitution generally not permitted
- Biosimilar education

# Recommended Policies to Increase Biosimilar Adoption

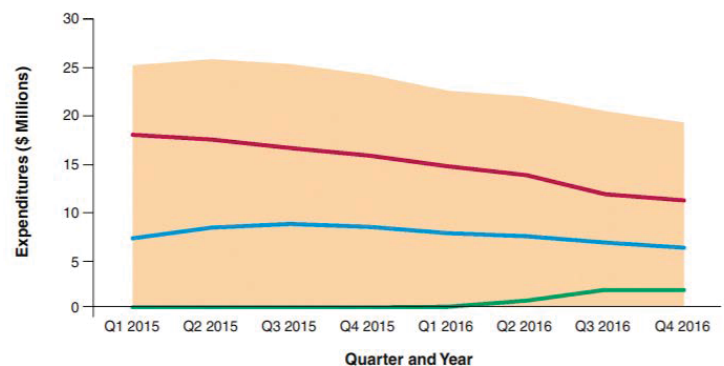
- Increase knowledge of biosimilars
- More competitive, sustainable pricing
- Clarity and support for switching
  - Burden is currently on prescriber
  - IT infrastructure needed
  - EMA should decide on substitution (e.g., interchangeability)
  - Naïve vs. established users

# Impact of Competition on GCSF Expenditures: USA

## Clinics



## Nonfederal Hospitals



All GCSF Products Tbo-filgrastim Filgrastim Filgrastim-sndz

## Infliximab expenditures

- Biosimilar infliximab launched Q4 2016
- Market share was approximately 2% in 2017
  - 60% growth at end of 2017
  - Access to biosimilar infliximab in the commercial insurance space was limited due to exclusionary contracting with insurers and providers
  - Lawsuit with Johnson & Johnson

<https://www.biopharma-reporter.com/Article/2017/08/04/Biosimilar-boost-for-Pfizer-but-Inflectra-share-just-2.3-of-US-market>

## FDA Commissioner's Speech on Biosimilars

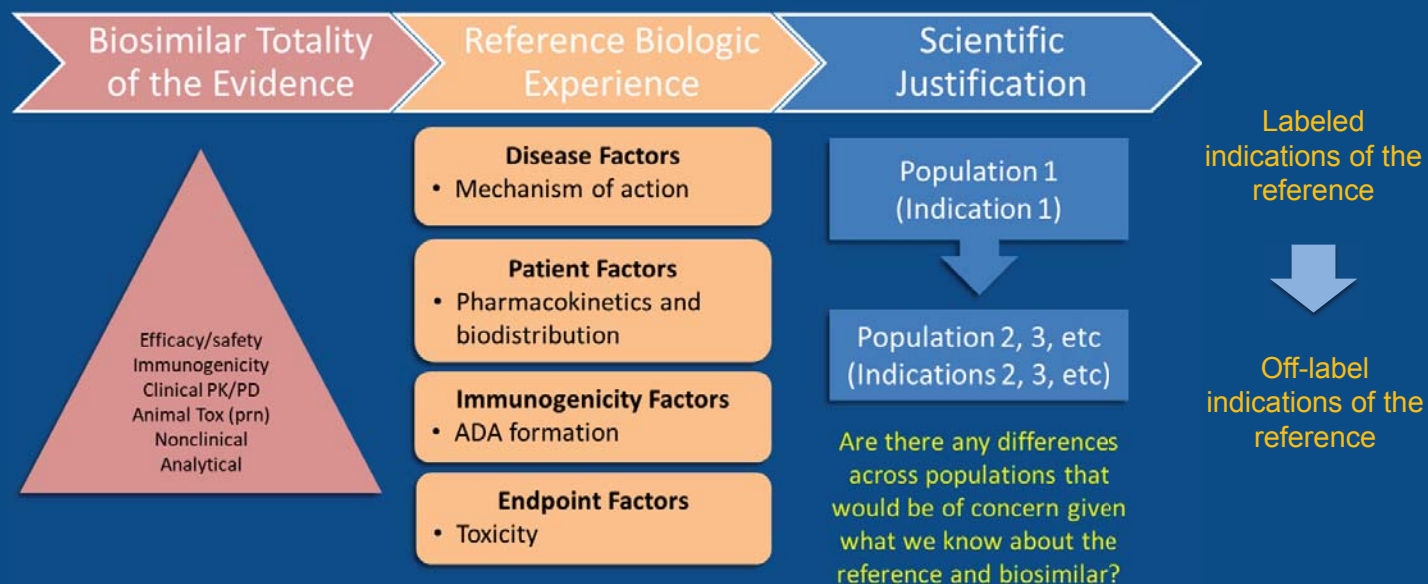
- “Current rebating and contracting practices – combined with the increased consolidation that we’re seeing in many segments of the drug supply chain – has produced some misaligned incentives.”
- “In the long run, the interests of patients, providers, and manufacturers are not well served by these arrangements, precisely because these practices encourage large list price increases to fuel the pricing schemes.”
- Questions/concerns:
  - Are these savings being passed on to the patients?
  - Does this pricing scheme help to improve access to biologics?
  - Are these short-term gains worth the long-term damage to the market?

<https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm>

# Future Regulations and Policies Affecting Uptake

- Interchangeability
  - Impact on substitution
- Off-label
  - A significant portion of antineoplastic utilization is for off-label purposes
  - Currently, CMS reimbursement is tied to approved compendia who apply a framework to make off-label decisions
  - The evidence framework to make decisions for reference products cannot be applied to biosimilars

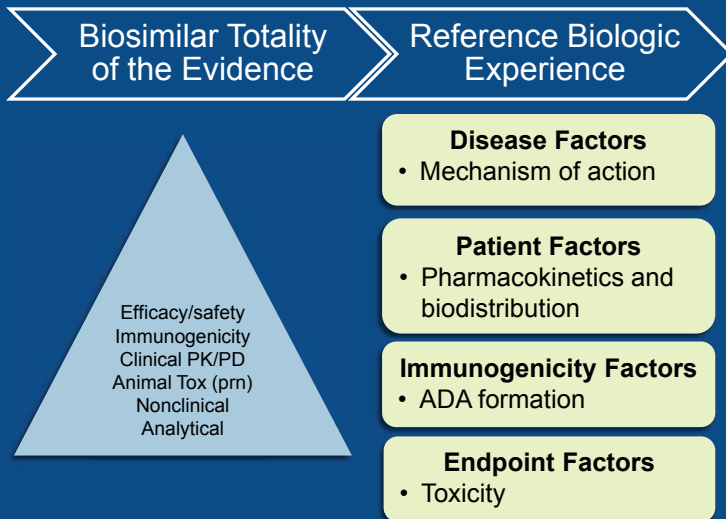
## Using the Extrapolation Framework to Make Off-label Determinations



European Medicines Agency. Concept paper on extrapolation of efficacy and safety in medicine development. March 19, 2013.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/04/WC500142358.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142358.pdf).  
 Weise M, et al. *Blood.* 2014;124(22):3191-3196.

# Case Study: Filgrastim-sndz

## Scientific Justification for Use of filgrastim-sndz in Treatment of Symptomatic Anemia in Patients with MDS



What Is Known About the Reference Product Between On-Label and Off-Label Indications	What Is Known About the Biosimilar
There is a single receptor (G-CSFR) by which G-CSF mediates its effect; the production of mature neutrophils is the same for neutropenia due to cytotoxic chemotherapy and for myelodysplasia	Filgrastim-sndz is highly similar to reference filgrastim; functional studies confirm that the binding affinity is comparable between products <sup>2</sup>
Clearance is mediated by neutrophils and bioavailability increases during periods of neutropenia; early PK studies of the reference and biosimilar typically included healthy volunteer	Studies of healthy volunteers (a more sensitive population as recognized by the FDA) demonstrated that filgrastim-sndz is bioequivalent to reference filgrastim
The overall immunogenicity of filgrastim is low	The overall immunogenicity of filgrastim-sndz is similarly as low as the reference product
Major adverse effects of filgrastim include injection site pain and bone pain;	The safety profile of filgrastim-sndz is similar to that of the reference product
Reports indicate that mutations in the G-CSFR may influence the development of a leukemic transformation	As previously indicated, the bioactivity of filgrastim-sndz is highly similar to that of the reference product

Li EC and Lobaina E. *J Manag Care Spec Pharm.* 2017 Dec;23(12):1227-1232

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## Summary

- Improvements within BsUFA are likely to help speed the approval of biosimilar agents
- A Biosimilar Innovation Plan to be unveiled by the FDA aims to improve the efficiency of biosimilar approvals
- Biosimilars in Europe have led to decreased costs and increased access to biologics
- Off-label utilization of biosimilars will need to be addressed
- Educational efforts aimed at improving stakeholder knowledge of biosimilars should continue

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# Questions?

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## FACULTY BIOGRAPHY

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**Director of Legislative Affairs**  
**Academy of Managed Care**  
**Pharmacy**

Reginia Benjamin has been the Director of Legislative Affairs for the Academy of Managed Care Pharmacy (AMCP) since April 2013, where she focuses on federal and state legislative issues impacting managed care and specialty pharmacy. She is the staff liaison to the Public Policy Committee, Legislative and Regulatory Action Committee and the State Advocacy Coordinator program. Prior to joining AMCP, she held positions in the health insurance and managed care industry as insurance department counsel, corporate in-house counsel for several insurance companies and trade association state lobbyist. She has served as an appointed industry representative on several statewide Commissions.

Ms. Benjamin has extensive experience with federal and state health insurance and managed care related laws as well as state regulations. She has testified before more than 30 state legislatures on insurance and pharmacy issues as well as before the National Association of Insurance Commissioners, National Black Caucus of State Legislators and the National Conference of Insurance Legislators.

Ms. Benjamin holds a B.S. in History Education from Hampton University and a J.D. from the University of Richmond. She is an active member of the Virginia state bar and admitted in the Commonwealth of Pennsylvania and the U.S. District Court for the Middle District of Pennsylvania.

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**Edward Li, PharmD, MPH, BCOP**  
**Professor**  
**University of New England College**  
**of Pharmacy**

Dr. Li earned his Doctor of Pharmacy degree from the Philadelphia College of Pharmacy and his Master of Public Health from the University of New England. He completed a Pharmacy Practice Residency at the University of Wisconsin Hospital and Clinics and an Oncology Pharmacy Practice Residency at the University of Maryland School of Pharmacy. Dr. Li is a Board Certified Oncology Pharmacist who maintains a practice with the New England Cancer Specialists, the region's largest oncology group, located in Scarborough, Maine and is currently a Professor at the University of New England College of Pharmacy. He also works with New Century Health, a leading innovator of quality and cost management programs, to develop cancer treatment pathways. Before joining UNE, he was the Oncology Pharmacy Manager at the National Comprehensive Cancer Network, a not-for-profit organization whose clinical practice guidelines in oncology are the standard of care in the United States. His research focuses on cancer pharmacoepidemiology, pharmacoconomics, and determining the value of cancer drugs and biologics.