BIOSIMILARS: REAL WORLD CONSIDERATIONS FOR PHARMACISTS

AMCP WEBINAR
NOVEMBER 7, 2019

AMGEN

THE U.S. MARKETPLACE WITH BIOSIMILARS IS REALLY TAKING OFF

U.S. Market Growth

EU Experience

Potential Savings

Sustainability

As more biosimilars reach the U.S. marketplace, we expect to see significant savings driven by competition. Biosimilar manufacturers can provide a wide range of attributes for patients and providers, including delivery devices, patient services, provider education, and commitment to reliable supply.

ELEMENTS CRUCIAL TO FOSTERING A ROBUST AND SUSTAINABLE MARKETPLACE WITH BIOSIMILARS OVER THE LONG TERM

Scientifically appropriate and robust regulatory standards strengthen stakeholder confidence

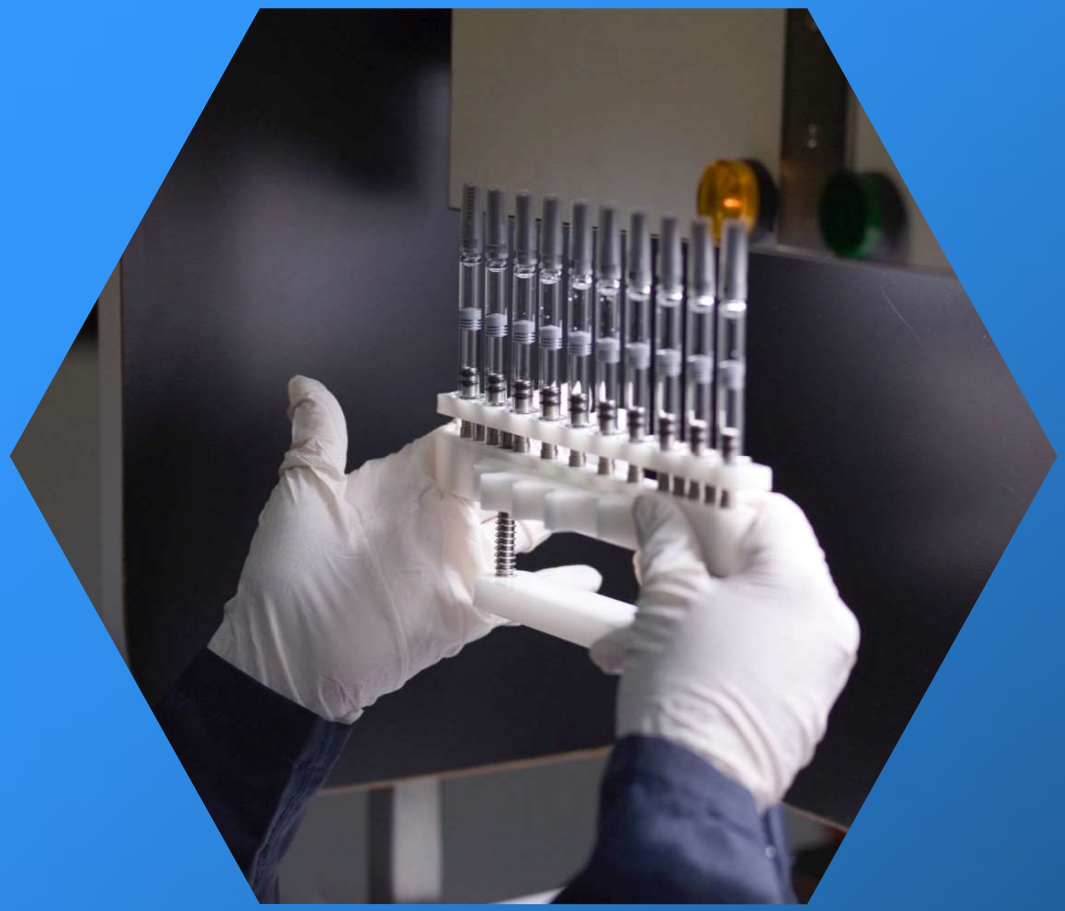
A market that encourages competition on a level playing field to achieve meaningful savings and long-term stability

Scientifically accurate educational outreach to drive uptake and proper use

A foundation of intellectual property as a vital component of a successful marketplace

STAKEHOLDER CONFIDENCE REQUIRES SCIENTIFICALLY APPROPRIATE STANDARDS

Scientifically appropriate and robust regulatory standards strengthen stakeholder confidence



REGULATORY APPROVAL STANDARDS

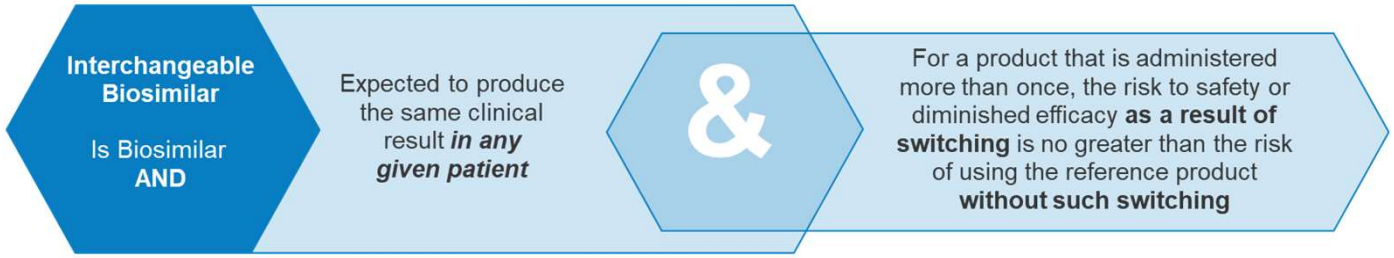
The success of biosimilars depends on the development and maintenance of **scientifically sound and robust standards for approval and manufacturing.** For biosimilars, the totality of evidence to demonstrate biosimilarity, including comparative analytical and clinical studies, is necessary to support licensure.

INTERCHANGEABILITY

Current **standards outlined in FDA guidance for demonstrating interchangeability are scientifically appropriate** and will serve to promote patient safety and build physician confidence.

SWITCHING AND INTERCHANGEABILITY

HOW DOES US LAW* DEFINE "INTERCHANGEABILITY" WITH RESPECT TO BIOSIMILARS?



Importantly, a designation as an interchangeable biosimilar :

- Requires *additional* data and information to scientifically support the statutory definition and automatic pharmacy-level substitution
- Does ***not*** imply anything about the quality of the product
  - Non-interchangeable biosimilars are held to the same quality standards as interchangeable biosimilars
- Is ***not*** required for physicians to prescribe a biosimilar product in place of the reference product to treatment-naïve patients or patients currently in treatment

FDA = Food and Drug Administration.

*The Biologics Price Competition and Innovation Act (BPCI Act) of 2009 created an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to (and in some cases also interchangeable with) an already FDA-approved biological product. FDA uses this definition of interchangeability when reviewing a request for an interchangeability designation.

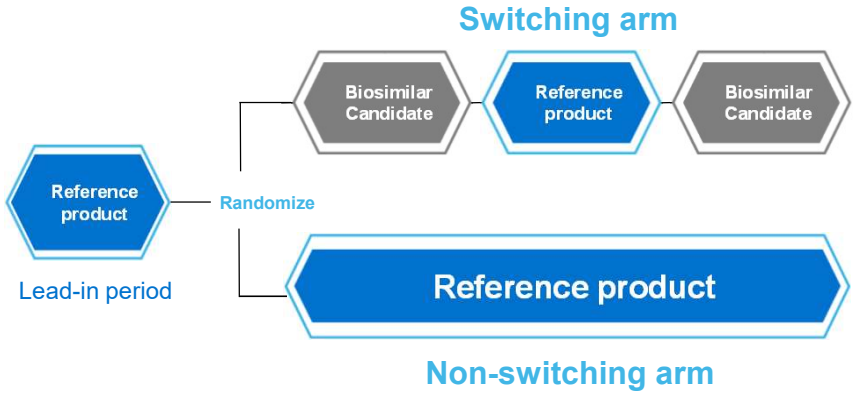
WHAT EVIDENCE SUPPORTS AN INTERCHANGEABLE DESIGNATION?

"can be expected to produce the same clinical result as the reference product in *any given patient*"

&

" 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*"

- **Scientific justification to support expectation of same clinical performance in all the reference product's conditions of use**
- **Presentation and device design differences must not adversely impact use or performance**



Integrated designs which serve to demonstrate biosimilarity and interchangeability are also acceptable

FDA. *Considerations in Demonstrating Interchangeability with a Reference Product. Guidance for Industry*. Published May 2019. Available at https://www.fda.gov/media/124907/download

WHAT DOES INTERCHANGEABILITY IN THE U.S. MEAN PRACTICALLY?

Interchangeable Biosimilar

Is Biosimilar **AND**

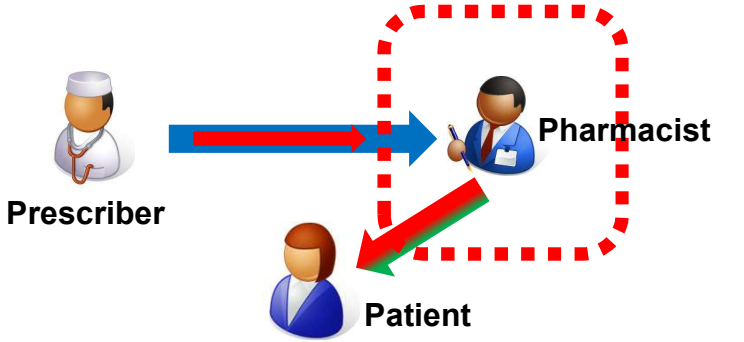
Expectation of the same clinical result ***in any given patient***

&

For a product that is administered more than once, the risk to safety or diminished efficacy **as a result of switching** is no greater than the risk of using the reference product **without such switching**

An interchangeable product may be **substituted for the reference product by a pharmacist *without the intervention of the prescriber***

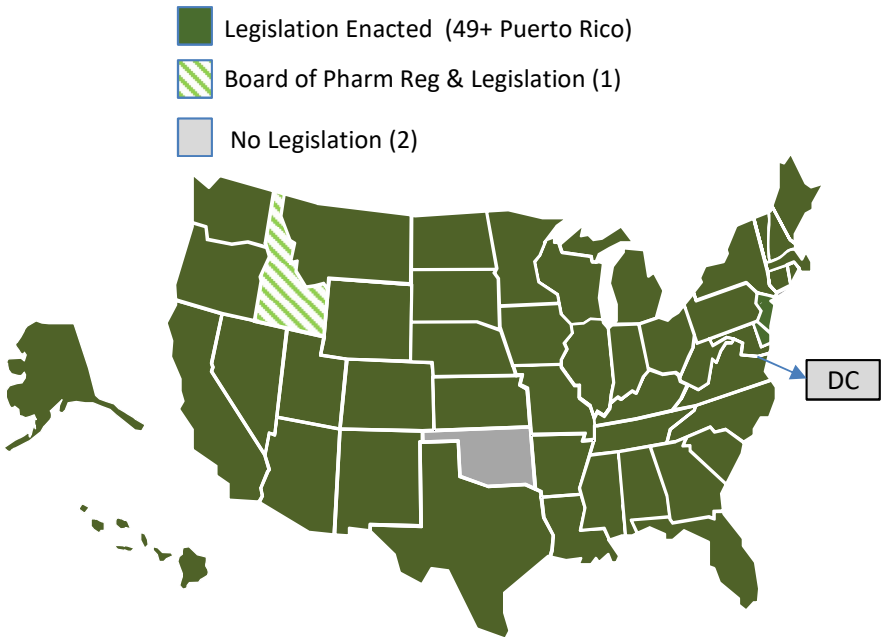
Pharmacy-Mediated Substitution



D Decision maker A Advisor I Implements decision

PHARMACY SUBSTITUTION OF INTERCHANGEABLE BIOSIMILARS

- Although the FDA designates a biosimilar as interchangeable, **US state pharmacy laws control substitution in the U.S.**[1]
- Once an interchangeability designation is acquired, a biosimilar may be **substituted for the reference product by a pharmacist without the intervention of the prescriber** in states that have approved legislation or regulations establishing state standards for biosimilar substitution[1,2]
- Since 2013, **a total of 49 states and Puerto Rico** have **enacted state pharmacy practice acts to address biologic subsitution**[1]



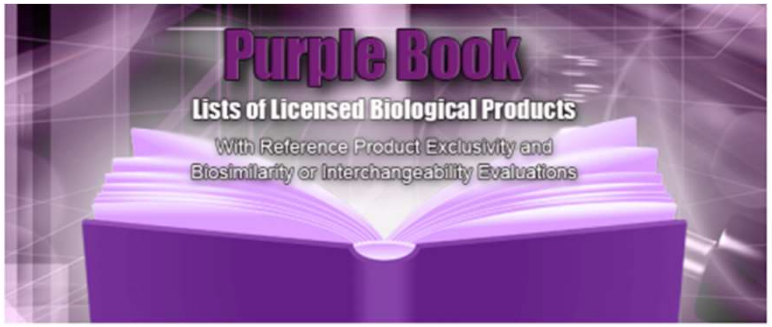
FDA = Food and Drug Administration.

1. NCSL. State Laws And Legislation Related To Biologic Medications And Substitution Of Biosimilars www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. October 22, 2018. Accessed December 11, 2018.

2. FDA. *Considerations for Demonstrating Interchangeability With a Reference Product.* Guidance for Industry. Published May 2019. Available at https://www.fda.gov/media/124907/download

For the most up-to-date information on state legislation related to biosimilars, visit the National Conference of State Legislatures (NCSL) website at: http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

THE PURPLE BOOK WILL BE USED IN THE U.S. AS A REFERENCE FOR HEALTHCARE PROVIDERS AND PATIENTS



The “Purple Book” lists biological products, including any biosimilar and interchangeable biosimilar products, licensed by FDA under the Public Health Service Act (the PHS Act).

- Date product was licensed
- Date of Product Exclusivity Expiry Date
- Whether product is a Biosimilar (B) or Interchangeable (I)

BLA STN	PRODUCT (PROPER) NAME	PROPRIETARY NAME	DATE OF LICENSURE (mo/day/yr)	DATE OF FIRST LICENSURE (mo/day/yr)	REFERENCE PRODUCT EXCLUSIVITY EXPIRY DATE (mo/day/yr)	INTERCHANGEABLE (I)/ BIOSIMILAR (B)
125118	abatacept	Orencia	12/23/05	NA	NA	
103575	abciximab	ReoPro	12/22/94	NA	NA	
125274	abobotulinumtoxinA	Dysport	04/29/09			
125057	adalimumab	Humira	12/31/02	NA	NA	
761071	adalimumab-adaz	Hyrimoz	10/30/18			B
761058	adalimumab-adbm	Cyltezo	08/25/17			B
761024	adalimumab-atto	Amjevita	09/23/16			B

INTERCHANGEABILITY AND SUBSTITUION OF BIOSIMILARS

Interchangeability of biosimilars around the world[1]			
USA[2] 	**Europe[3]** 	**Canada[4]** 	**Australia[5]** 
Defined in BPCI Act	Defined in consensus document	No definition	
FDA may approve a product as interchangeable	EMA does not have remit to designate interchangeability for purposes of substitution	Health Canada does not designate biosimilars as interchangeable for purposes of substitution	Australia's PBAC can designate biosimilars as interchangeable, known as "a-flagging"
Individual states control the act of pharmacy-level substitution	Interchangeability for purposes of substitution decisions reside within Member states	Interchangeability for purposes of substitution decisions reside with provinces	Payer body has exclusive authority to determine substitution of biosimilars at the pharmacy level
FDA issued final guidance in May 2019	Some regulatory agencies issued statements in 2015 clarifying support for prescriber-supervised switching between a reference product and a biosimilar		
49 US states and Puerto Rico have passed legislation addressing biosimilar substitution (as of August 2019)	Pharmacy-level substitution for biosimilars in not widely practiced in any EU country	Health Canada does not support automatic substitution	Substitution of biosimilars recommended as its default policy
BPCI Act = Biologics Price Competition and Innovations Act of 2009; EMA = European Medicines Agency; EU = European Union; PBAC = Pharmaceutical Benefits Advisory Committee.			

1. Interchangeability of biosimilars in the US and around the world Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(2):97-8. 2. US FDA. May 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry
3.International policies for interchangeability, switching and substitution of biosimilars. http://gabionline.net/Reports/International-policies-for-interchangeability-switching-and-substitution-of-biosimilars 4.Government of Canada. Fact Sheet Biosimilars. https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html
5. Australia's PBAC recommends substitution of biosimilars. http://www.gabionline.net/Biosimilars/General/Australia-s-PBAC-recommends-substitution-of-biosimilars

DEFINITIONS OF SUBSTITUTION, SWITCHING, AND INTERCHANGEABILITY – TERMINOLOGY MATTERS

AUTOMATIC SUBSTITUTION

- Practice where one drug is dispensed in place of another at the pharmacy level, without consulting the prescribers[1,2,‡]

SWITCHING

- Physician may elect to prescribe one medicine in place of another with the same therapeutic intent.[2]
- In Europe, in the context of biosimilars, the term "switching" is used synonymously with the term "interchangeable"[1]

INTER-CHANGEABILITY

- In the US, "interchangeable" is defined by statute to means that a biosimilar product is expected to behave the same in "any given patient" and that there is no negative impact resulting from alternating or switching between the biosimilar product and the reference product.[3] Most US state pharmacy laws permit automatic substitution at the pharmacy of only biosimilars that FDA has deemed "interchangeable".[4]

*In some US states, there is ongoing dialogue regarding post-dispensing notification and documentation; †private organization management of substitution may vary based on formulary decisions and other factors; ‡prescribers may indicate "Dispense As Written" and patients may request the originally prescribed biologic medicine.

Slide References

1. EuropaBio. *Guide to Biological Medicine.* Published 2014.
2. CADTH. *International Policies on the Use of Biosimiliar Drugs.* 2018.
3. FDA. *Considerations in Demonstrating Interchangeability with a Reference Product. Guidance for Industry*. Published May 2019.
4. National Conference of State Legislatures. *State Laws and Legislation Related to Biologic Medication and Substitution of Biosimilars*. www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx October 22, 2018. Accessed December 11, 2018.
5. European Commission. *What You Need to Know about Biosimilar Medicinal Products.* Published 2013.

PHARMACOVIGILANCE OF BIOLOGICS

POST-APPROVAL PHARMACOVIGILANCE IS IMPORTANT FOR ALL BIOLOGICS, INCLUDING BIOSIMILARS[1]

Rigorous pharmacovigilance is essential for all biologics to protect patients and facilitate adverse events to be quickly detected, reported, and attributed to the correct product and manufacturer[1,2]

It is important that all biologics have a unique, distinguishable identifier to accurately identify the product in the medical record.

Safety monitoring should take into account the safety or effectiveness concerns associated with the reference biologic product. [1]

Safety monitoring should have the ability to differentiate between adverse events associated with the biosimilar product vs. those associated with the reference drug or other biosimilars, not simply a product class[1]

Pharmacovigilance mechanisms should facilitate targeted regulatory action, when warranted, To ensure patient access.

1. FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry*. Published April 2015.
2. FDA. *Nonproprietary Naming of Biological Products Update: Guidance for Industry.* Published March 2019.

IMPORTANCE OF PHARMACOVIGILANCE

- Pharmacovigilance is important for all biologics, including biosimilars
  - No two biologics are identical
  - Because biologics are extremely sensitive to manufacturing and handling conditions, problems may emerge for specific products or product batches
- It is important that all biologics have unique, distinguishable identifiers so that doctors, pharmacists, and patients can tell them apart and accurately identify the product in the medical record
- Adverse events must be quickly detected and reported, and attributed correctly
- Safety monitoring should be able to differentiate events associated with specific products, not simply a product class
- Pharmacovigilance mechanisms should facilitate targeted regulatory action in order to ensure patient access

US Food and Drug Administration. Guidance for industry: nonproprietary naming of biological products. 2019 https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf, and 2019 https://www.fda.gov/media/121316/download

MULTIPLE APPROACHES TO IMPROVING PHARMACOVIGILANCE FOR BIOLOGICAL PRODUCTS EXIST GLOBALLY

Distinguishable Nonproprietary Naming

FDA will designate a proper name comprised of the "core name" and a distinguishing suffix that is devoid of meaning for all[1]:

- New originator biologics
- Biosimilars
- Interchangeable biosimilars

Goal: facilitate accurate identification of products by healthcare practitioners and patients, improve pharmacovigilance, and help minimize inadvertent pharmacy substitution of non-interchangeable biosimilar products

Pharmacovigilance Legislation[2]

Passage of Directive 2010/84/EU and Regulation 1235/2010 aimed at reducing the number of ADRs in the EU through:

- the collection of better data on medicines and their safety;
- rapid and robust assessment of issues related to the safety of medicines;
- effective regulatory action to deliver safe and effective use of medicines;
- empowerment of patients through reporting and participation;
- increased levels of transparency and better communication.

Requirements Include: clear identification of suspected product by **name** and **batch** number

Guideline on Good Pharmacovigilance Practices (GVP) entered into force in 2016 and recommended recording of name and batch number

1. FDA Draft Guidance on Nonproprietary Naming of Biological Products: Update. Guidance for Industry. March 2019. Available at https://www.fda.gov/media/121316/download.
2. EU Pharmacovigilance framework and GVP guidelines. Available at https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance/legal-framework-pharmacovigilance.

FDA NAMING CONVENTION FOR BIOLOGICAL PRODUCTS

The proposed suffix should be:

- Unique
- Devoid of meaning
- Consist of 4 lowercase letters
- Nonproprietary

The proposed suffix should not:

- Be false or misleading
- Include numerals and other symbols
- Include abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order
- Look similar to or be capable of being mistaken for the name of a currently marketed product
- Look similar to or otherwise connote the name of the license holder
- Be too similar to any other FDA-designated nonproprietary name suffix

US Food and Drug Administration. Guidance for industry: nonproprietary naming of biological products. 2017 https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf, and 2019 https://www.fda.gov/media/121316/download

SCIENTIFICALLY ACCURATE EDUCATIONAL OUTREACH BUILDS STAKEHOLDER CONFIDENCE AND IS KEY TO SUPPORTING BIOSIMILAR ACCEPTANCE AND USE

Scientifically accurate educational outreach to drive uptake and proper use

The success of biosimilars will be supported by scientifically accurate educational outreach

- **Education** about biosimilars for healthcare providers (HCPs), patients, payers, employers, and the organizations that represent them **is key to supporting biosimilar acceptance and use**.
- **HCPs should understand the scientific data needed to attain regulatory approval** for biosimilars in order to make confident treatment decisions.
- **HCPs should be able to trust that an approved biosimilar will be as safe and effective as its originator product**. In some markets, the approval process does not always require globally established standards for demonstrating biosimilarity, including comparative testing with an originator product. Therefore the clinical profile of non-comparable biotherapeutic products may not necessarily be expected to be the same as the originator biologic and remains unknown.
- **Amgen supports evidence-based medicine and encourages physicians to consider carefully** the risks and **benefits of switching stabilized patients** between originator and biosimilar medicines.

THANK YOU FOR YOUR ATTENTION.

QUESTIONS?