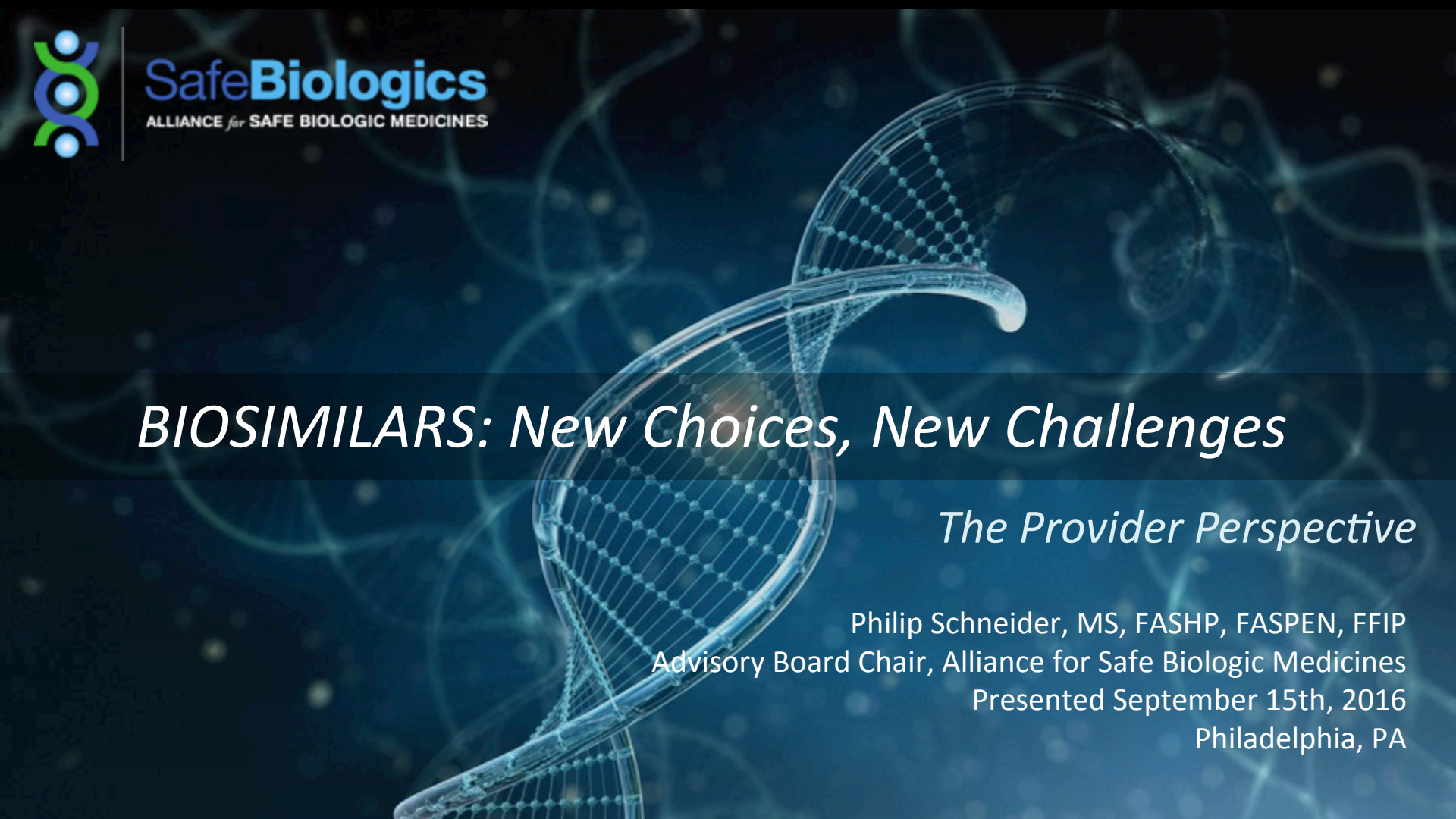


BIOSIMILARS: New Choices, New Challenges

The Provider Perspective

Philip Schneider, MS, FASHP, FASPEN, FFIP
Advisory Board Chair, Alliance for Safe Biologic Medicines

Presented September 15th, 2016
Philadelphia, PA

About The Alliance for Safe Biologic Medicines (ASBM)

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

Philip J. Schneider, MS, FASHP, FASPEN, FFIP: Professor and Associate Dean, University of Arizona College of Pharmacy – Phoenix

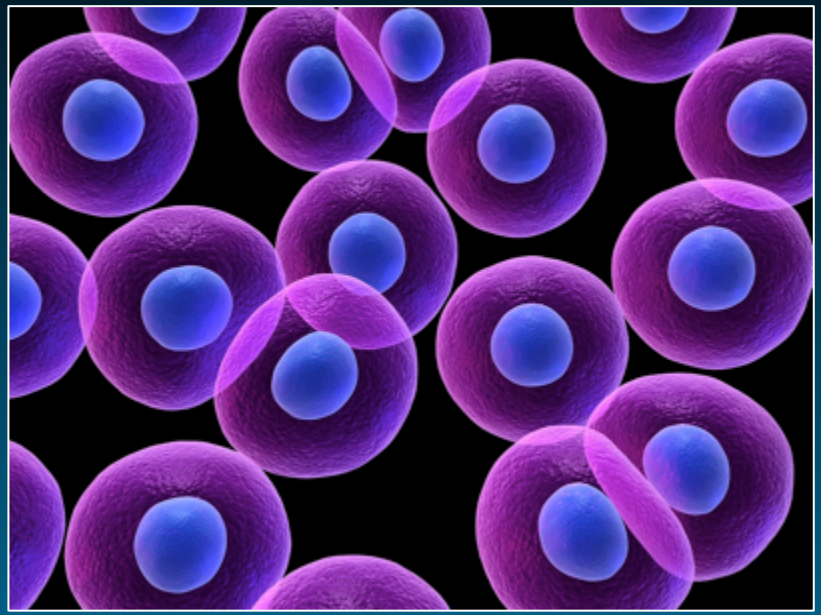
Michael Reilly, Executive Director
michael@safebiologics.org

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


Biologic Medicines

What is a Biologic Medicine?

A **biologic medicine** is
a **substance** that is
made **from** a **living organism**
rather than a chemical compound.

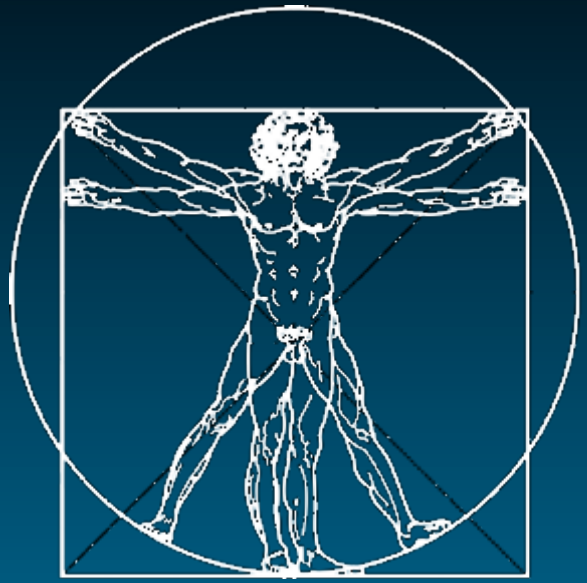


Benefits of Biologic Medicines

- Biologic medicines treat patients with autoimmune disorders), neurological disorders, and all types of cancers.

- Biologics developed to target and modify the underlying causes of disease, potentially altering the course of the disease rather than simply treating symptoms.

- The development of new biologic medicines may be the best hope for effectively treating diseases for which there are currently no cures.



Biologic vs. Chemical Medicines

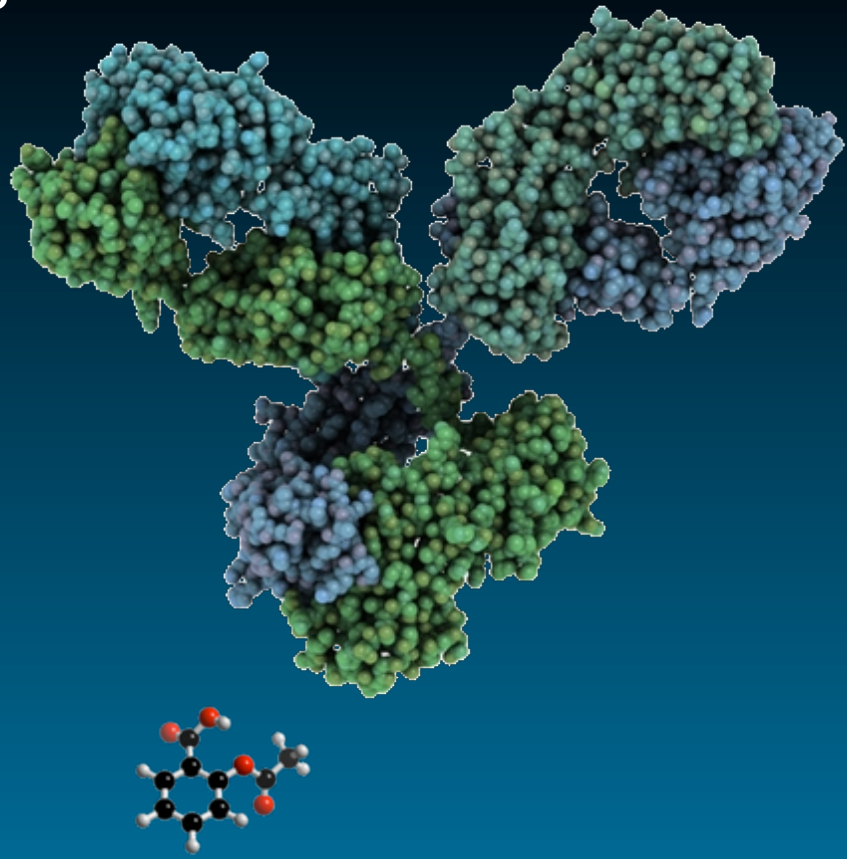
STRUCTURE: more complex, cannot be completely characterized or copied

STABILITY: susceptible to light, heat, denaturing / degradation

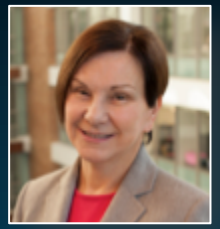
SENSITIVITY: even small manufacturing changes can cause changes in efficacy and/ or adverse effects

DRIFT: can change with time

SIZE: significantly larger, potential for immunogenic reactions

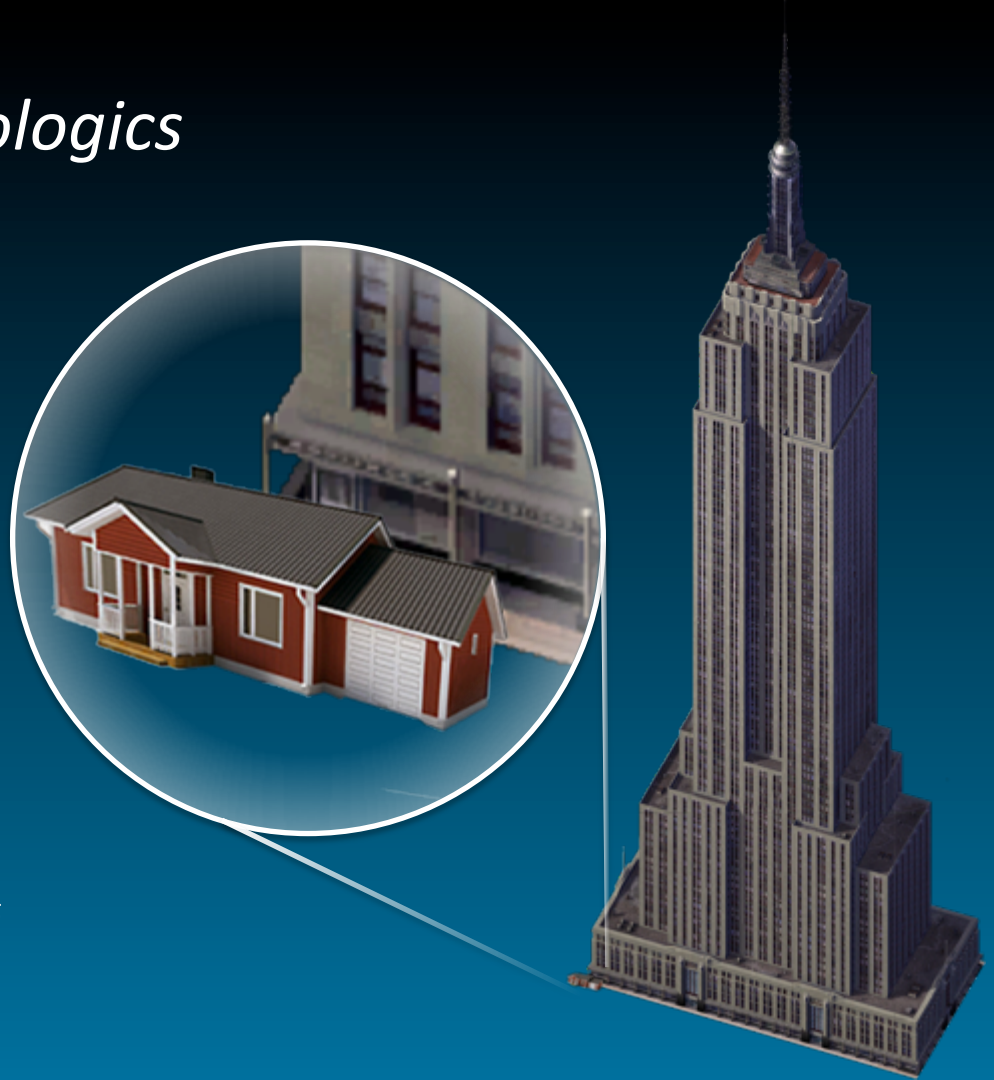


Size and Complexity of Biologics



"Biologics [and biosimilars] are like the Empire State Building, compared to a regular drug, which is like a small house"

-Dr. Janet Woodcock,
Director of the Center for Drug Evaluation and Research (CDER), FDA
February 4, 2016

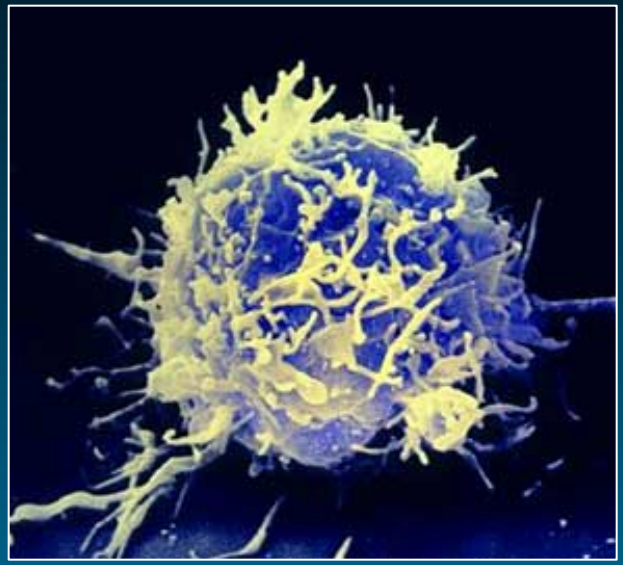


Potential for Immunogenicity is a Concern

All biologic medicines are fairly large molecules, sometimes resembling a virus, and have the potential to induce unwanted antibody responses (i.e., be immunogenic).

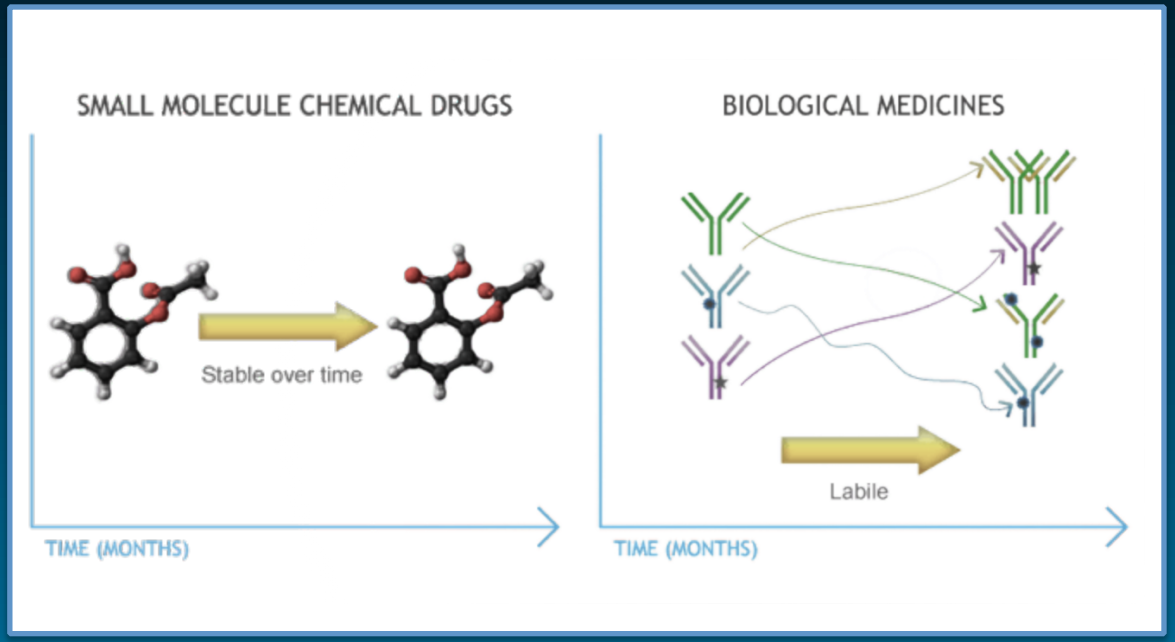
The unwanted immune response may be of no consequence for a patient, or of serious consequence.

- Immunogenicity may neutralize the medicine, minimizing or eliminating its intended effect.
- One of the main concerns is that the immune system may attack the endogenous protein, making the patient's condition worse than before the medicine was introduced.



Stability of Biologics?

- While chemical medicines are relatively stable, biologics can undergo many modifications during storage, and their composition (which of the molecule's variations are present) will change over time.



Sensitivity: Potential for Degradation of Biologics

- Avoid rapid temperature change- increase temperature gradually.
- Avoid multiple temperature cycles.
- Avoid excess force (shaking, shearing forces).
- Be aware of device composition (needle gauge, potential for contamination).
- Consult manufacturer stability data.

Biosimilars

What is a Biosimilar?

- Biosimilars are sometimes incorrectly referred to as “generic” biologics.

- However, unlike with generic copies of chemical medicines, their greater complexity and fact that they are made using living cells means biologic medicines cannot be copied exactly.
  It can only ever be “similar” to its reference biologic.

- “Interchangeable” biosimilars are those which pharmacists will potentially be able to substitute.

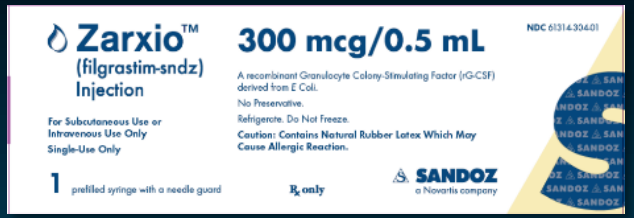
Three Biosimilars Approved in U.S.

March 6, 2015: Zarxio (filgrastim-sndz)
15% discount over reference product

April 6, 2016: Inflectra (infliximab-dyyb)
US sale price unknown.

August 30, 2016: ii (etanercept-szzs)

<u>NONE are "INTERCHANGEABLE"</u>

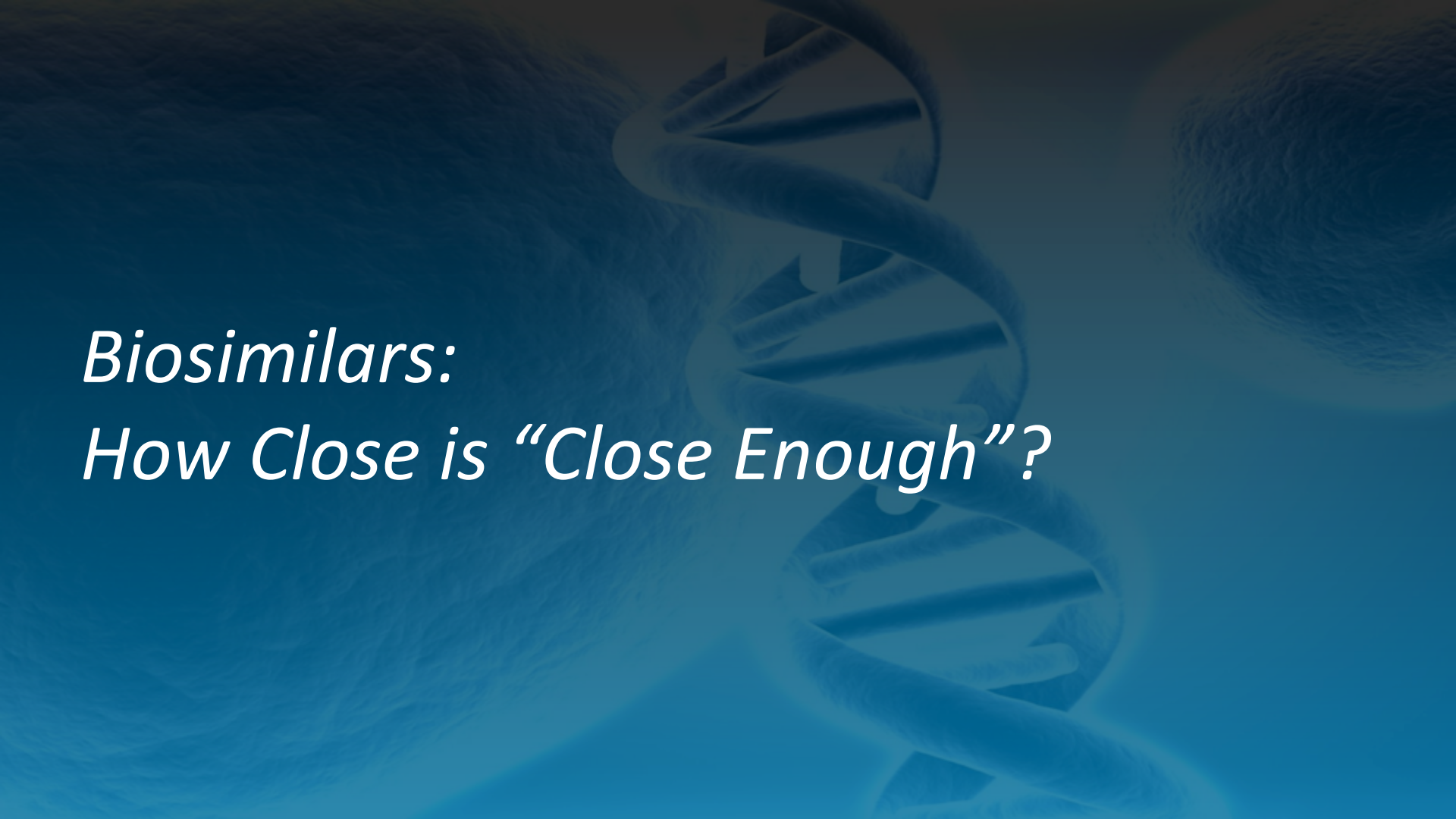


What Does "Interchangeable" Mean?

A higher regulatory standard to meet. More data is required.

An "INTERCHANGEABLE" :

1) Must be biosimilar ("highly similar" to reference product).
2) Must have same clinical result expected as with reference product.
3) Must create no additional risk to patient when switching back and forth between itself and reference product.
4) May be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.


Biosimilars:
How Close is “Close Enough”?

All Biologics Contain Minor Differences

- Biosimilars cannot be, and thus are not expected to be, direct copies of originator (also known as “reference”) biologics.

- FDA defines a biosimilar as “a biological product that is *highly similar to the reference product notwithstanding minor differences in clinically inactive components.”*

- **Minor differences** are expected and permitted but must be demonstrated not to be “clinically meaningful” in regards to safety, purity, or potency.

So, Aren't All Biologics Biosimilars, Then?

- No. A biologic will be grown from the same cell line, but will have a natural range of variability from lot to lot.
- By contrast, a biosimilar to that reference product is a new molecule, made from a different cell line, grown through different processes, that has a starting point well outside this range.

So, Aren't All Biologics Biosimilars, Then?

- How close it can get to the range- and performance- of the reference product will determine whether it is a different biologic, a biosimilar (highly similar), or an interchangeable (same results expected, no additional risks if switched).

- In 2009, a manufacturer scaled up production of a biologic, Myozyme, and though it was grown from the same cell line, the differences took it outside its expected range. It was required to file a Biologics License Application as a new product, and was approved for same indications as Myozyme in 2014.

Biosimilar Naming

Some Benefits of Distinguishable Naming:

CLEAR PRODUCT IDENTIFICATION - Distinguishable from reference product, and other approved biosimilars.

CLEAR COMMUNICATION - between physician, patient and pharmacist

CLEAR PRESCRIBING & DISPENSING - Helps prevent inadvertent and inappropriate substitution.

BETTER PHARMACOVIGILANCE - proper attribution of adverse events.

INCREASED MANUFACTURER ACCOUNTABILITY - differentiating suffixes (preferably tied to manufacturer or marketing authorization holder name) will accomplish this.

WHO Biologic Naming Proposal

- The World Health Organization has identified clear biologic and biosimilar naming as an issue of global importance; they are working to establish an international standard.
- I have participated several of these WHO meetings, including the most recent on April 12th and upcoming meeting on October 18th.
- Similar biologics will be differentiated from each other by use of a **random 4-letter code** known as a "Biological Qualifier" (BQ).


World Health Organization

Biological Qualifier
An INN Proposal

Programme on International Nonproprietary Names (INN)

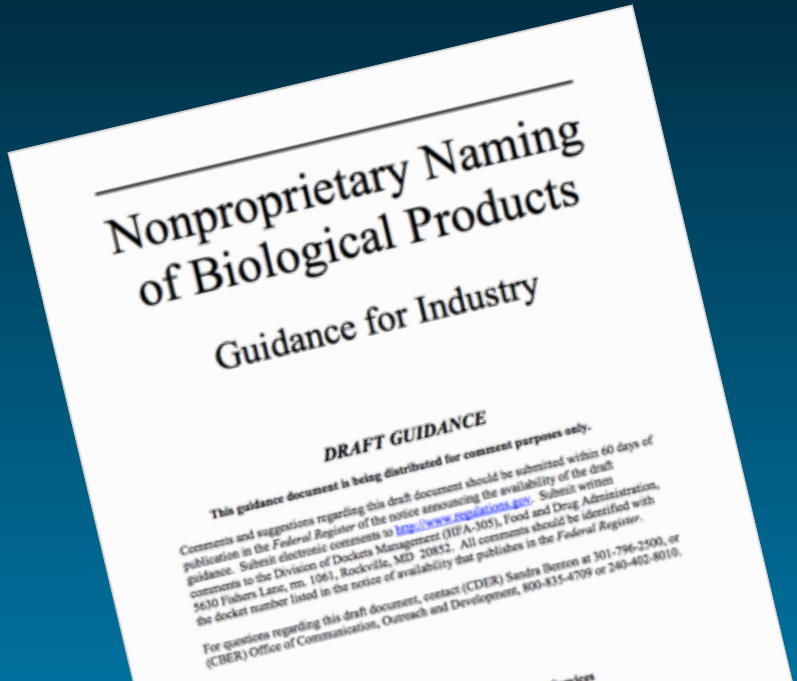
Technologies Standards and Norms (TSN)
Regulation of Medicines and other Health Technologies (RMT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

August 2015: FDA Released BQ-Compatible Naming Guidance

- "There is a need to clearly identify biological products to improve pharmacovigilance and, for the purposes of safe use, to clearly differentiate among biological products that have not been determined to be interchangeable."

- Guidance calls for a "core name" (for biosimilar and interchangeable products, the name of the reference product) with a BQ-Compatible four-letter differentiating suffix "devoid of meaning"

- FDA has solicited comments from stakeholders on issues, including the merit of meaningful rather than random suffixes.



Nonproprietary Naming of Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

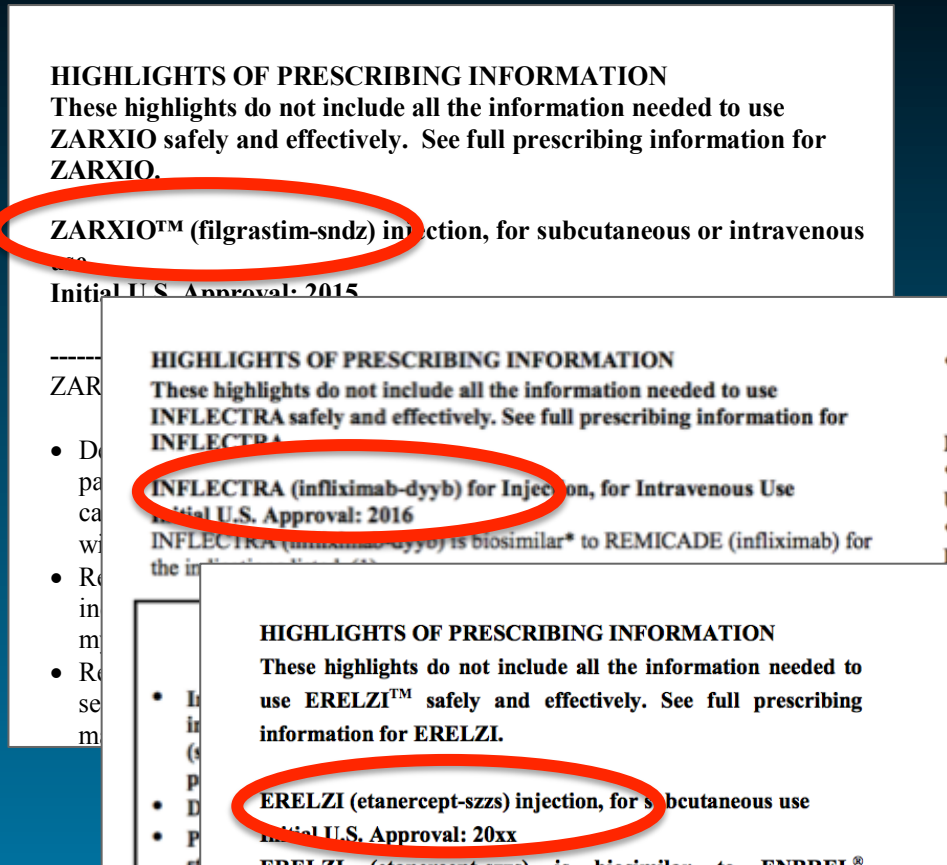
For questions regarding this draft document, contact (CDER) Sandra Benton at 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

All Three U.S. Biosimilars have Distinguishable Names.

- Each use DIFFERENTIATING SUFFIX but with ONE **KEY DIFFERENCE:**

  Zarxio (filgrastim-sndz) uses Suffix based on name of manufacturer (entity responsible for safety and efficacy of product)

- **Inflectra (infliximab-dyyb) and Erelzi (etanercept-szzs) use a random suffix,** similar to the WHO's Biological Qualifier (BQ) proposal.



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

Initial U.S. Approval: 2015

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

INFLECTRA (infliximab-dyyb) for Injection, for Intravenous Use

Initial U.S. Approval: 2016

INFLECTRA (infliximab-dyyb) is biosimilar* to REMICADE (infliximab) for the

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

ERELZI (etanercept-szzs) injection, for subcutaneous use

Initial U.S. Approval: 20xx

Gathering the Perspectives of Providers Around the World

Canadian Physician Survey (December 2014) n= 427

U.S. Physician Surveys
September 2012: n=376
February 2015 (Labeling): n=400
November 2015: n=400

E.U. (France, Italy, Spain, UK) Physician Survey
November 2013: n= 470

U.S. Pharmacist Survey
September 2015: n=401

Latin America (Argentina, Brazil, Colombia, Mexico) Physician Survey
May 2015: n=399

All surveys available at www.SafeBiologics.org

Surveys Show Broad Physician Support for Distinguishable Naming

79% of Canadian physicians support Health Canada issuing distinct names. (2015)

94% of Latin American Physicians consider WHO's BQ Proposal to be "useful" in helping patients receive the correct medicine. (2015)

66% of US physicians support FDA issuing distinct names. (2015)

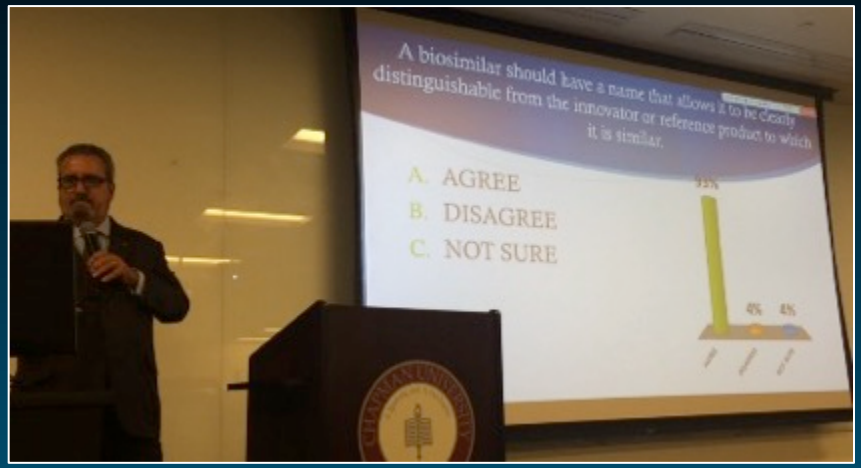
Pharmacists and Distinguishable Naming

- Pharmacists have traditionally avoided look-alike, sound-alike drug names.
- Even if a drug is considered similar, it should be easily identified.
- Industry has been asked in the past to change drug names to avoid confusion and errors.

Pharmacist Perspectives on Biosimilars

U.S. Pharmacist Associations (APhA and ASHP) have opposed distinct nonproprietary names, including the WHO and FDA proposals.

- We found through CE courses that many pharmacists were generally more supportive of distinguishable naming than their professional associations.



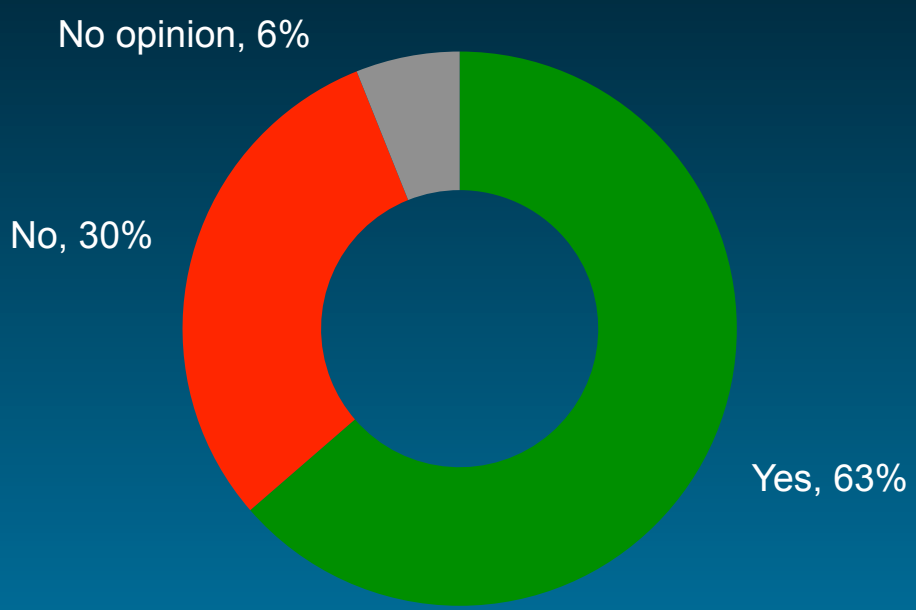
(At right, a poll of pharmacists showing strong support for distinct names- Irvine, CA course)

- These experiences led ASBM to quantify these findings with a 401-PHARMACIST SURVEY

ASBM U.S. Pharmacist Survey: Does a Shared INN Imply…

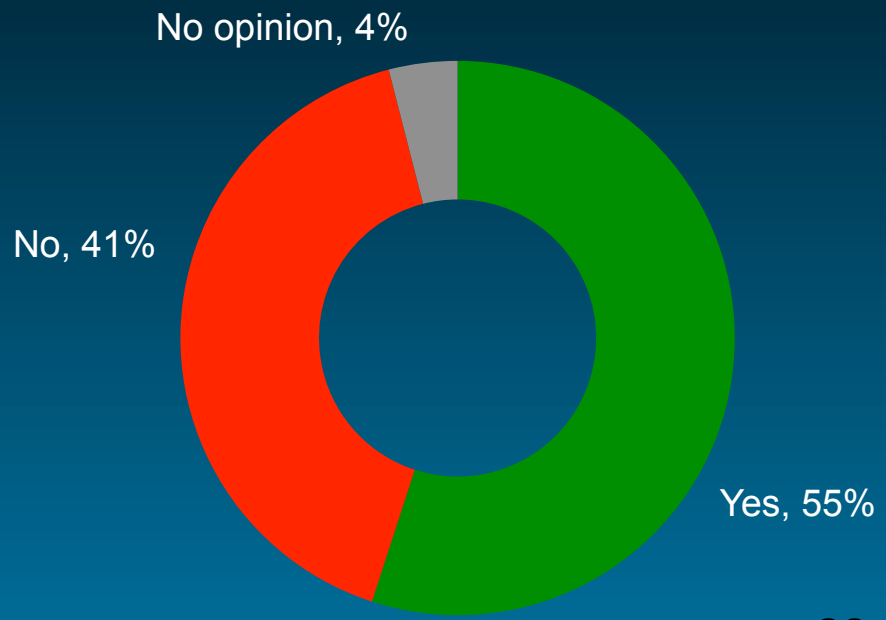
…Structural Identicality?

(this is not possible)



…Approval for the Same Indications?

(this may or may not be the case)



U.S. Pharmacist Survey: Distinguishable Naming

23%
OPPOSE
FDA issuing distinguishable names

68%
SUPPORT
FDA issuing distinguishable names

8%
No Opinion

15%
PREFER
RANDOM
SUFFIX

77%
PREFER MANUFACTURER-BASED
SUFFIX

8%
No Opinion

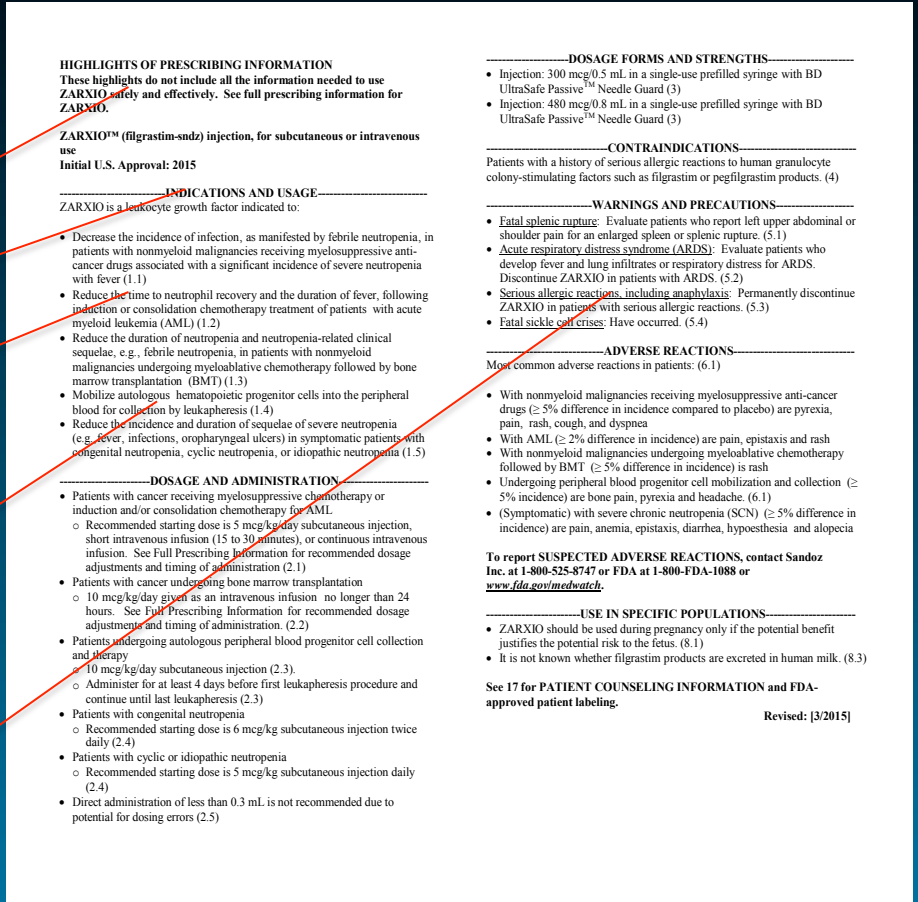
ASBM Survey of 401 U.S. Pharmacists, September 2015

Biosimilar Labeling

Concerns Surrounding Zarxio's Biosimilar Labeling

Some concerns surrounding insufficient transparency in Zarxio's labeling:

- It is not identified as a biosimilar.
- No data used to demonstrate biosimilarity is included.
- Not specified for which indications approval was based on trial data, or extrapolation.
- Data from innovator product is not identified as such.



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 blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)

----------DOSAGE AND ADMINISTRATION----------

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.1)
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3).
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Direct administration of less than 0.3 mL is not recommended due to potential for dosing errors (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 300 mcg/0.5 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard (3)
- Injection: 480 mcg/0.8 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard (3)

----------CONTRAINDICATIONS----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue ZARXIO in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions in patients: (6.1)

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia and headache. (6.1)
- (Symptomatic) with severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

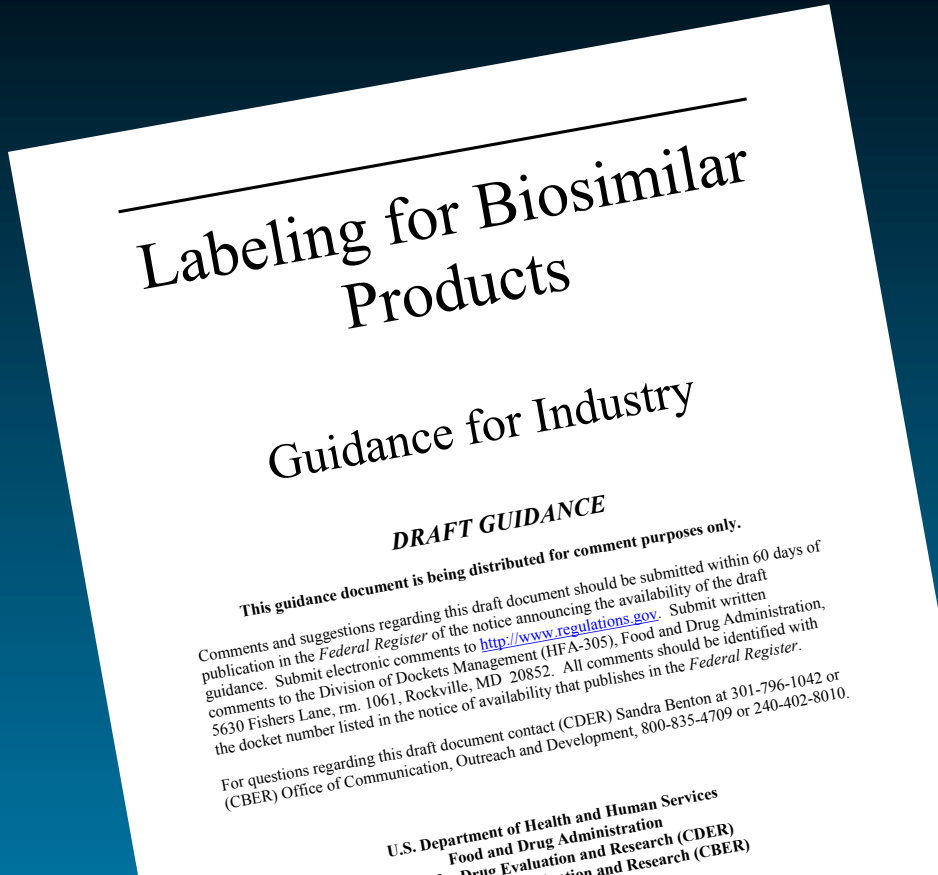
- ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- It is not known whether filgrastim products are excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [3/2015]

FDA Labeling Guidance

On March 31st , 2016, the FDA released its long-awaited Draft Guidance on Labeling, which begins to address some, though not all of these providers' concerns.



Labeling for Biosimilar Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Drug Evaluation and Research (CDER)
Biologics Evaluation and Research (CBER)

ASBM Surveys: What Do Providers Want In Biosimilar Labeling?

	Physicians (Feb 2015) (n= 400)	**Pharmacists** (Sept. 2015) (n =401)	**Included in Zarxio labeling?**	**Included in FDA draft labeling guidance?**
	Rated as *important* or *very important*			
ID product as a biosimilar	90%	81%	X	✓
Name of biosimilar's reference product	77%	71%	X	✓
Analytical data used to demonstrate biosimilarity	82%	71%	X	X
Clinical data used to demonstrate biosimilarity	83%	71%	X	X
Indications for which originator is approved, but biosimilar is not	79%	76%	X	✓
Approved indications studied or extrapolated?	80%	76%	X	X
Interchangeable with originator product?	79%	88%	X	✓
Identify source of data: Originator or Biosimilar	79%	69%	X	X

1 Feb. 2015 Survey of 400 U.S. physicians

2 Sept. 2015 survey of 401 U.S. pharmacists

Biosimilar Substitution

Substitution Policy in the U.S.

CONGRESS

- Sets Legal definition
- Interchangeable: substitution without physician intervention

FDA

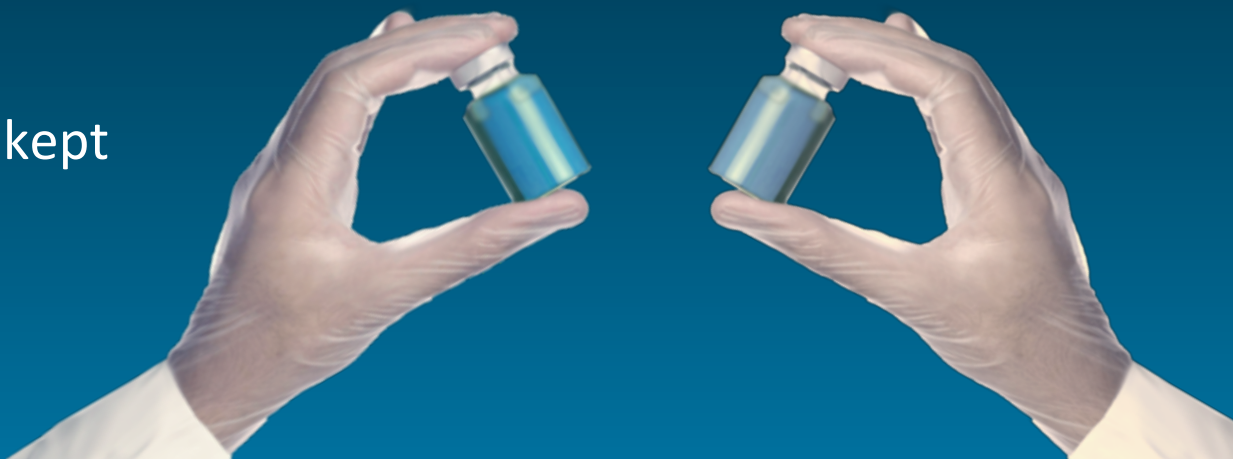
- Makes Scientific decisions
- Sets Interchangeability criteria

STATES

- Decides what pharmacists are allowed to do

Issues Surrounding Biosimilar Substitution

- Under what circumstances may a pharmacist substitute a biosimilar without the involvement of the physician?
- What communication is required between pharmacist and:
  - Physician
  - Patient
- What records must be kept of the substitution?



How Important is Communication of a Biosimilar Substitution?

85% *of Canadian physicians consider it "very important" or "critical"*

77% *of EU Physicians consider it "very important" or "critical"*

80% *of US physicians consider it "very important" or "critical"*

87% *of Latin American Physicians consider it "very important" or "critical"*

How Important is "Dispense as Written" (DAW) Authority?

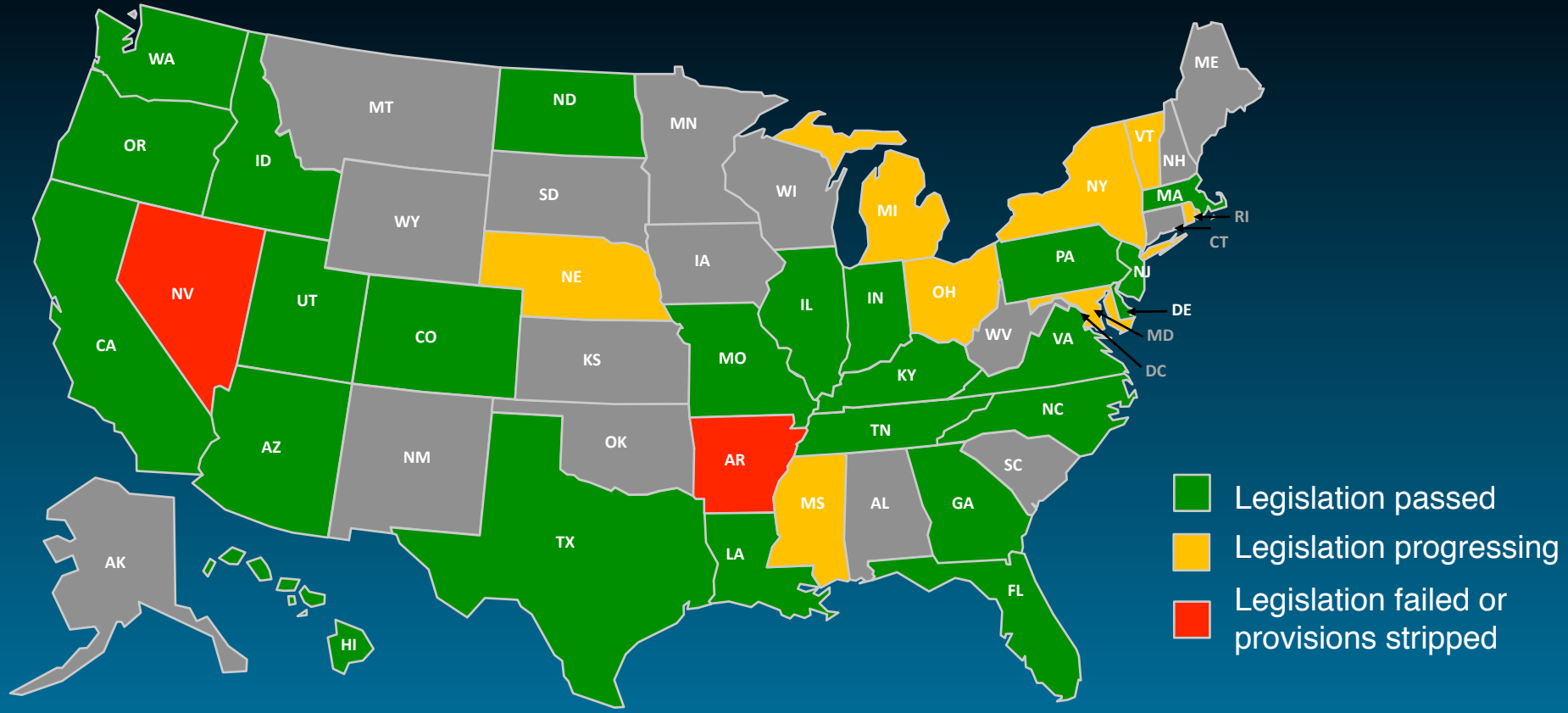
80% of Canadian physicians consider it "very important" or "critical" (2014)

74% of EU physicians consider it "very important" or "critical" (2013)

82% of US physicians consider it "very important" or "critical" (2012)

85% of Latin American physicians consider it "very important" or "critical" (2015)

Physician-Pharmacist Communication Requirements by US State



Rev. 09/14/16

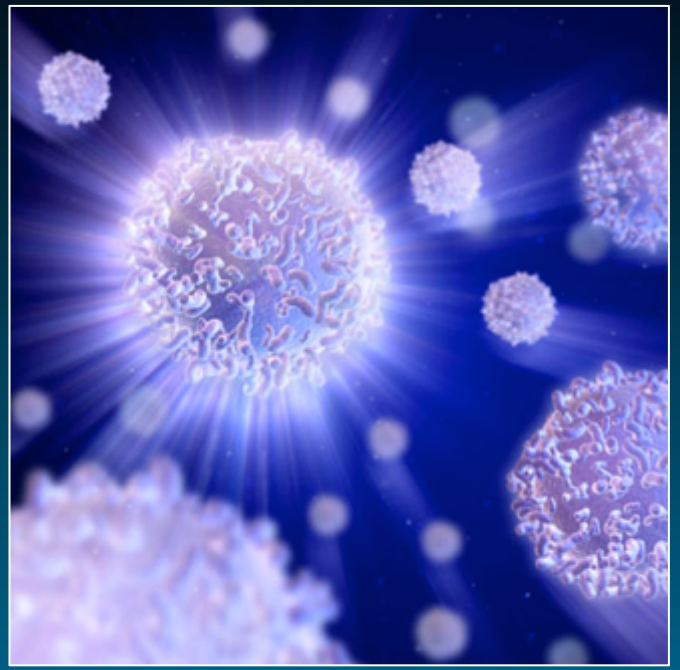
Pennsylvania Law

S. 514, Signed into law as Act no. 95 on July 20, 2016

- A pharmacist MAY substitute a biological product for a prescribed biological product only if:
  - FDA has determined it to be interchangeable
  - Prescriber does not designate verbally or in writing that substitution is prohibited
  - Person presenting the prescription receives notification of such substitution
- Pharmacist communicates to physician within 3 days which product was dispensed (except refills).

Summary

Biologics are advanced therapies FAR MORE COMPLEX and SENSITIVE to manufacturing differences and their environment than chemical drugs, necessitating special care and handling.

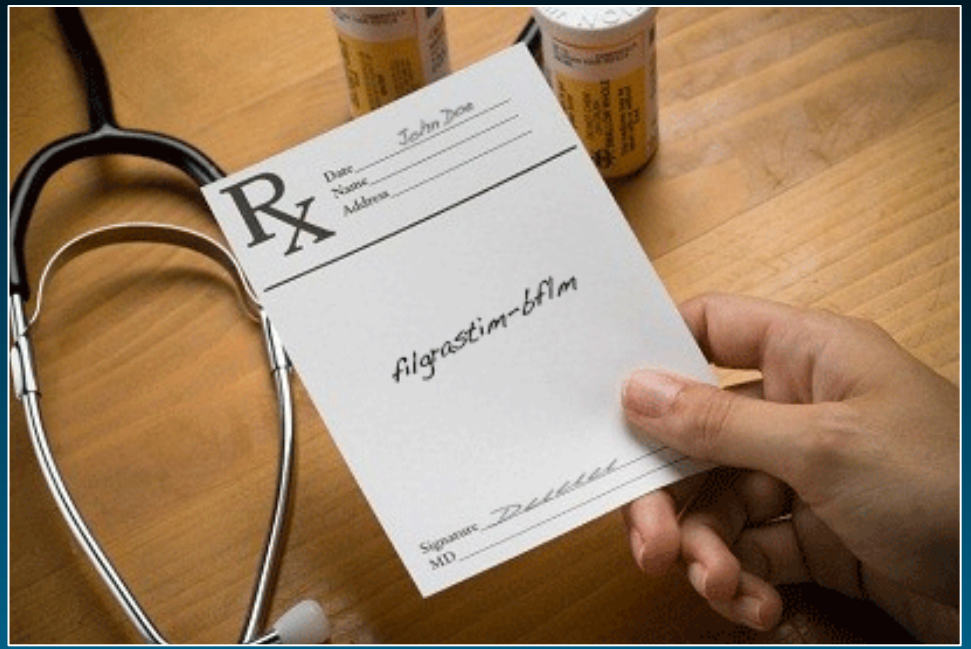


Summary

Biosimilars are SIMILAR to their reference product but NOT IDENTICAL; even minor differences between two similar biologics may create unexpected effects such as unwanted immune responses.

Summary

CLEAR PRODUCT IDENTIFICATION is important for tracking safety and efficacy of all biologics, including biosimilars, leading regulators are making this a priority.



Summary

In order for biosimilars to be widely adopted, patients and their health care providers must have CONFIDENCE in them.

Summary

TRANSPARENCY in LABELING (especially regarding interchangeability and indication extrapolation) is important to pharmacists and physicians.

Summary

Good COMMUNICATION and COLLABORATION between pharmacists and physicians allows maintenance of accurate patient records, and aids in accurate long-term tracking of safety and efficacy.


SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES
Thank You For Your Attention