SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES

The Fundamentals of Biosimilars: What Every Physician and Pharmacist Will Need To Know

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

Presented at St. Charles Health System, Bend OR on July 31, 2015

About The Alliance for Safe Biologic Medicines (ASBM)

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

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

Michael Reilly, Executive Director
michael@safebiologics.org

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

“The Four Pillars”

ASBM’S GUIDING PRINCIPLES

PRIORITIZING PATIENT SAFETY

LEVERAGING WHAT WE HAVE LEARNED

PROMOTING PHARMACO-VIGILANCE

KEEPING HEALTHCARE PROVIDERS RELEVANT

ASBM Physician Surveys

(Dermatologists- Endocrinologist- Oncologists- Nephrologists- Neurologists- Rheumatologists)

U.S. Physician Survey (September 2012): 376 physicians

E.U. Physician Survey (November 2013): 470 physicians

Canadian Physician Survey (November 2014): 427 physicians

U.S. Labeling Survey (February 2015): 400 physicians

Latin American Survey (May 2015): 399 physicians

To learn more about ASBM surveys, visit www.SafeBiologics.org

Recent ASBM Activity

Fall 2014: Present country-specific European survey results to Italian Health Ministry in Rome and Spanish Health Ministry in Madrid.

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

February 2015: Conduct survey of 400 U.S. physicians on issue of transparency in biosimilar labeling.

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

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

May 2015: Conducted educational courses on biosimilars for 180 Pharmacists in NY and CA.

June 2015: Released Latin American survey results (399 physicians in 4 countries) at DIA 2015 meeting

Presentation Objectives

1. Discuss the basic science and manufacturing of biologic medicines
2. Define biosimilars and explore how they differ from generic drugs for purposes of patient care, pharmacovigilance, and pharmacy practice.
3. Discuss key regulatory and policy considerations.

Biologic Medicines

What is a Biologic Medicine?

A **biologic medicine** is a **substance** that is made **from** a **living organism** or its products and is used in the prevention, diagnosis, treatment, or cure of a disease. Biologic medicines include:

- antibodies
- vaccines
- interleukins (these can regulate immune responses)
- hormones
- blood and blood products

At a molecular level, biologic medicines are often 200–1000 times the size of a chemical drug molecule and are far more complex structurally. They are highly sensitive to handling and their environment.

Biologics are more difficult to characterize and manufacture than chemical drugs.

Due to their size and sensitivity, biologic medicines are almost always injected into a patient's body.

Benefits of Biologic Medicines

- Biologic medicines have made a significant difference in the lives of patients with serious illnesses, including cancer, blood conditions, auto-immune disorders such as rheumatoid arthritis (RA) and psoriasis, neurological disorders like multiple sclerosis (MS), and Colorectal Cancer (CRC).

- By understanding the mechanisms of diseases, companies have developed biologic medicines 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

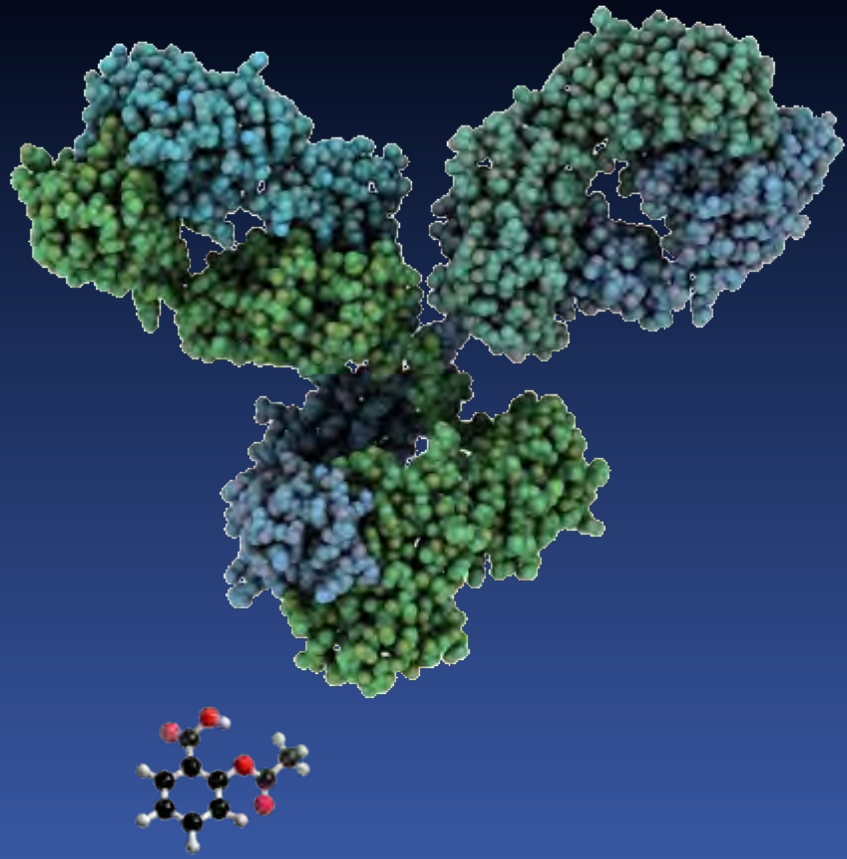
SIZE: significantly larger, potential for immunogenic reactions

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



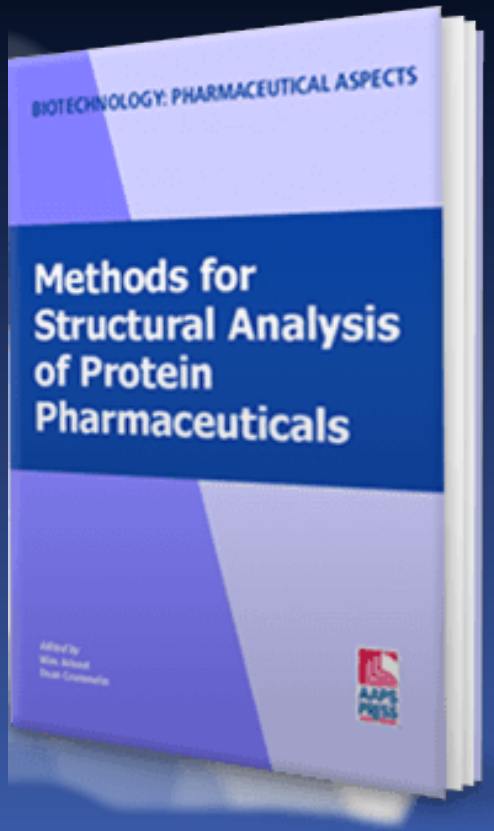
Proteins: Size, Structure & Complexity

	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size	Aspirin 21 atoms	hGH ~ 3000 atoms	IgG Antibody ~ 25,000 atoms
Complexity	Bike ~ 20 lbs	Car ~ 3000 lbs	F16 Jet ~ 25,000 lbs (without fuel)

Source: Genentech

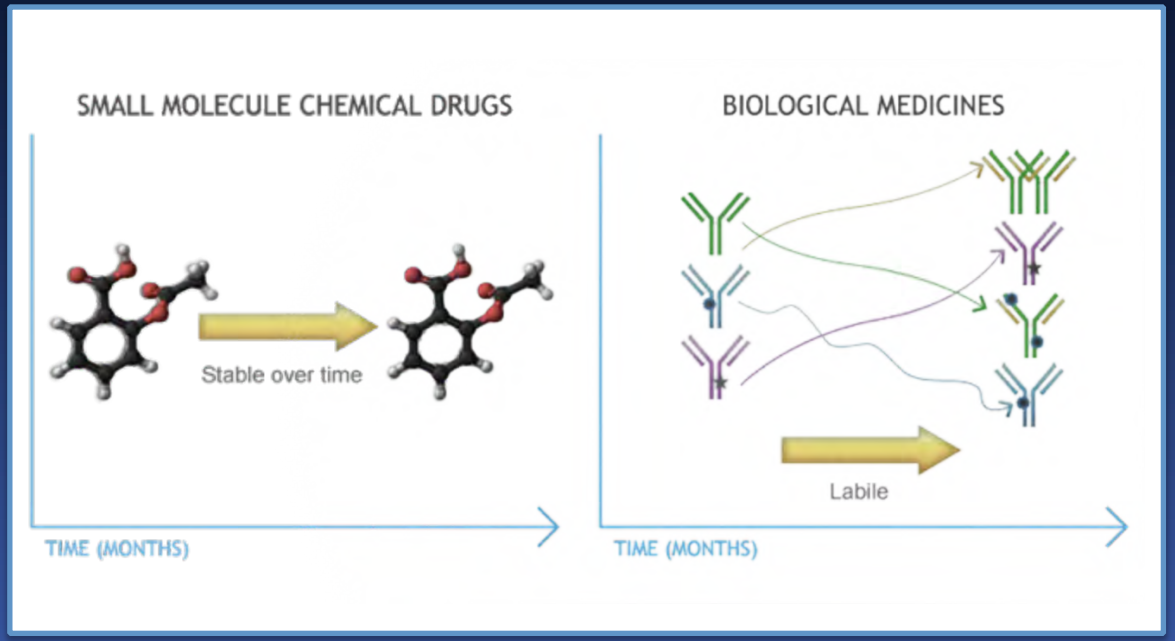
Complete Characterization is Impossible

- The complexity and sensitivity of biologics, their heterogenous nature, and their propensity to change over time, make characterization to the last atom impossible with current scientific knowledge and tools.
- To learn more about characterization of biologics, please consult ***International Journal of Pharmaceuticals, 2003, November, 266, 3-16***



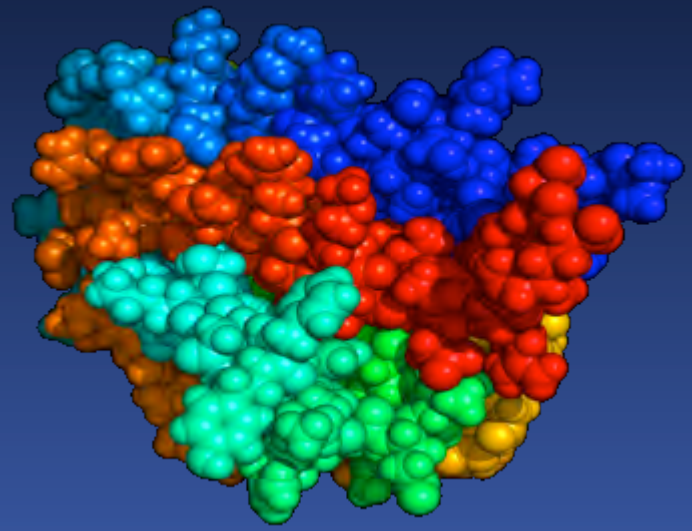
Stability of Biologics?

- 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.



Advantages of Large Size/Complexity of Biologics

- More precise fit to a large target (disease)
- Can interact with multiple targets (such as binding to two receptors) simultaneously
- Large molecule can stay in body longer



One Disadvantage of Large Size/Complexity: Immunogenicity

- Biologics have provided new options in the prevention and treatment of diseases in which previous therapies treated only the symptoms. However, because of their complexity, biologics are associated with additional risks. The most important of these risks is the potential to cause immunogenicity.

- Immunogenicity occurs when the immune system in the human body mounts an attack when a foreign substance enters the body. For example, when we catch a common cold (i.e. rhinovirus) or the flu (i.e., influenza virus), our body responds by attacking these viruses, thereby neutralizing them.

Immunogenicity: Causes and Monitoring

- Antibody reactions cannot be predicted via other means (e.g., animal studies), which is why clinical data are necessary.
- Processes and conditions could influence molecular structures in unexpected ways, leading to an unwanted immunogenic reaction.
- Monitoring patients for an immune reaction to the biologic is important both before and after regulatory approval.

Potential for Immunogenicity is a Major 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.

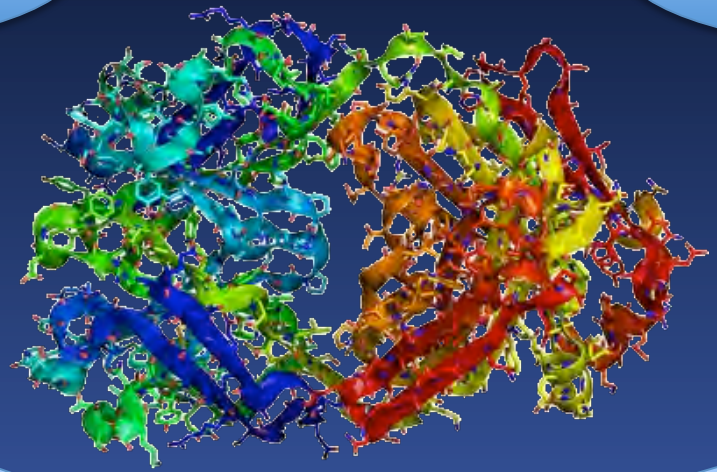
- Immunogenicity may neutralize the medicine, minimizing or eliminating the intended effect of the medicine.
- One of the main concerns is that the immune system may attack the endogenous protein, making the patient's condition worse than before the medicine was introduced.

Sensitivity of Biologics:
Potential for Degradation During Storage and Handling of Biologics

DILUTION

TEMPERATURE CHANGE

FILTRATION



SHAKING

ADSORPTION

SHEARING FORCES

LEACHING

OXYGEN EXPOSURE

METAL EXPOSURE

SILICON EXPOSURE

Potential for Degradation During Preparation

- **TEMPERATURE CHANGE**:
  Removing product from refrigeration can cause aggregation, precipitation.
- **ADDING DILUTENT:**
  Introduction of metal ions, silicon, oxygen can result in oxidation, catalysis, aggregation.
- **RECONSTITUTING:**
  Shaking, interaction with container, shearing forces can result in denaturing, unfolding, aggregation, hydrolysis, deamination.
- **INTRODUCTION TO INFUSION BAG:**
  Absorption, exposure to oxygen, silicon, and metal ions, leaching, shearing forces, etc., can result in denaturing, unfolding, aggregation, hydrolysis, deamination.

Minimizing 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.


From Biologics….
…to Biosimilars

What is a Biosimilar?

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

- However, unlike with generic copies of chemical medicines, the 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.

Europe Has Led the Way on Biosimilars

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

The USA is Now Beginning to Catch Up with Europe…

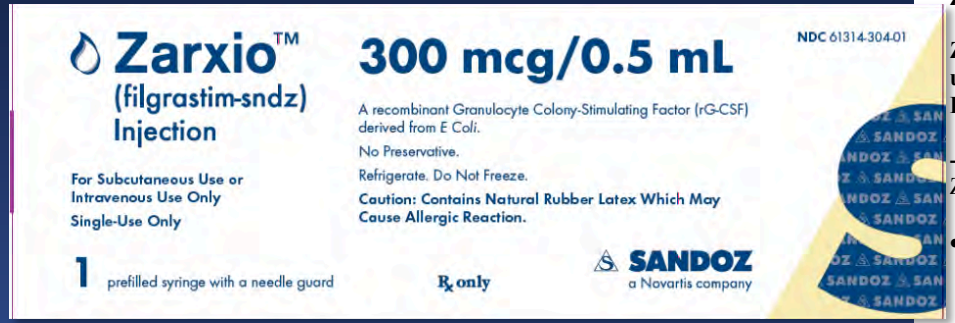
Benefits of Biosimilars

- Increased therapeutic options
  - Put U.S. patients on par with patients in Europe and Canada.
  - More treatment choices for physician and patient.
- Potential for cost savings
  - Unlike generics, which save 40-80%, due to higher development costs biosimilars are expected to save payers 15-30%[1]

1 Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4).120-6. DOI: 10.5639/gabij.2012.0103-4.036

March 6: First Biosimilar Approved in U.S.

- *Zarxio (filgrastim-sndz)*



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

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

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

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

FDA Approval of More Biosimilars is Expected Shortly

- On March 17, FDA's Arthritis Advisory Committee was set to meet to review Remsima, a biosimilar to Remicade (infliximab) – used to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis. Meeting postponed.
- This is the first monoclonal antibody (MaB) to seek approval from FDA under its approval pathway. Approved in EU and Canada, although for different indications.
- FDA approval is sought for all indications for which the innovator product has approval.

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FDA sets date for Celltrion biosimilar of Remicade

DAILY NEWS | FEBRUARY 10, 2015

KEVIN GROGAN

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Advisors to the US Food and Drug Administration will meet next month to review Celltrion's biosimilar of Johnson & Johnson and Merck & Co's anti-inflammatory blockbuster Remicade.

The FDA's Arthritis Advisory Committee will gather on March 17 to discuss the South Korean-based group's Remsima, its version of Remicade (infliximab). The filing, in August, was the first for a monoclonal antibody using the agency's new biosimilar pathway.

FDA

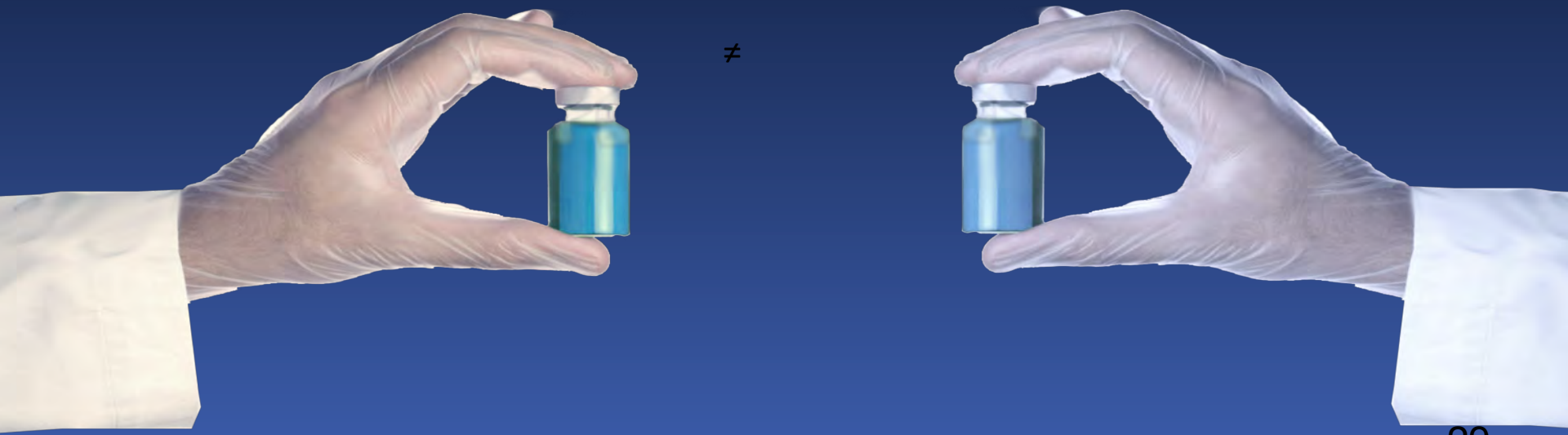
Celltrion is seeking to get approval for Remsima in the same therapeutic indications as Remicade

Related Links

Biosimilars:
How Close is “Close Enough”?

Remember: Biologics are made in living cells and are highly complex so they cannot be exactly copied.

Thus, Biosimilars are NOT Identical to their reference product…….They can only be "SIMILAR"



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.

FDA April 28th Guidance

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

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Monday, May 04, 2015

FDA WEEK - 05/01/2015

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

Posted: April 30, 2015

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

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

FDA April 28th Guidance, Continued

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

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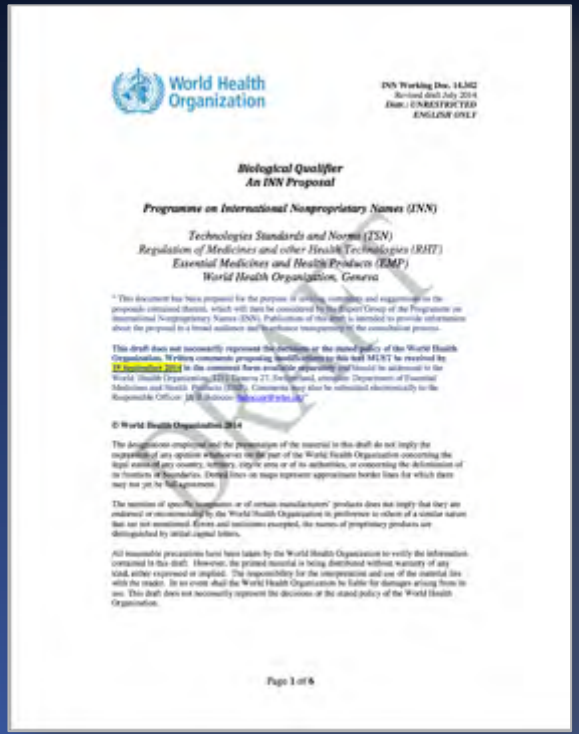
Biosimilar Naming

June: WHO Naming Meeting to Finalize BQ Proposal

- The WHO has proposed adding a unique, random 4-letter code called a Biological Qualifier (BQ) to the INN of all biologics, including biosimilars, to differentiate them from their reference products.

- Adherence to the BQ System is voluntary. A similar system is already in place in Japan. FDA has not yet weighed in on naming.

- ASBM chairman Dr. Harry Gewanter and its Advisory Board Chair, pharmacy professor Dr. Philip Schneider, participated in this meeting.



World Health Organization

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

Biological Qualifier
An INN Proposal

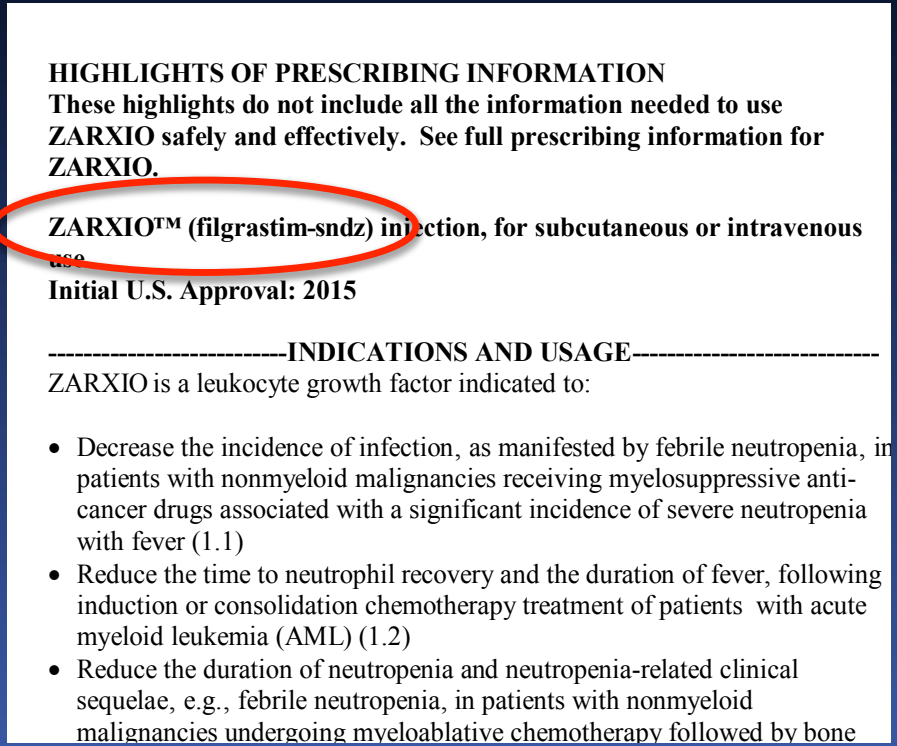
Programme on International Nonproprietary Names (INN)

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

Page 1 of 6

First U.S. Biosimilar has a Distinguishable Name.

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



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- 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

Benefits of Distinguishable Naming:

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

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

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

Benefits of Distinguishable Naming, Continued:

ACCURATE TRACKING

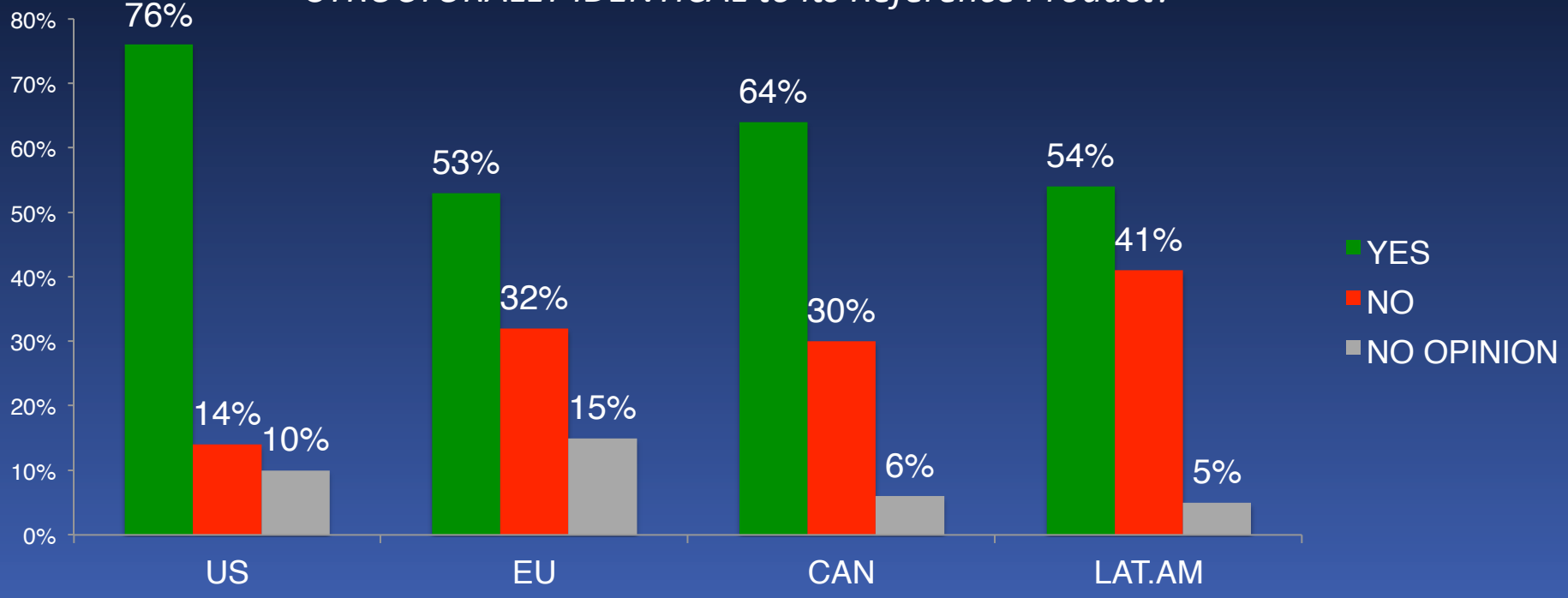
Distinguishable names ensure proper attribution of adverse events, and aid in long term tracking of safety and efficacy.

MANUFACTURER ACCOUNTABILITY

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

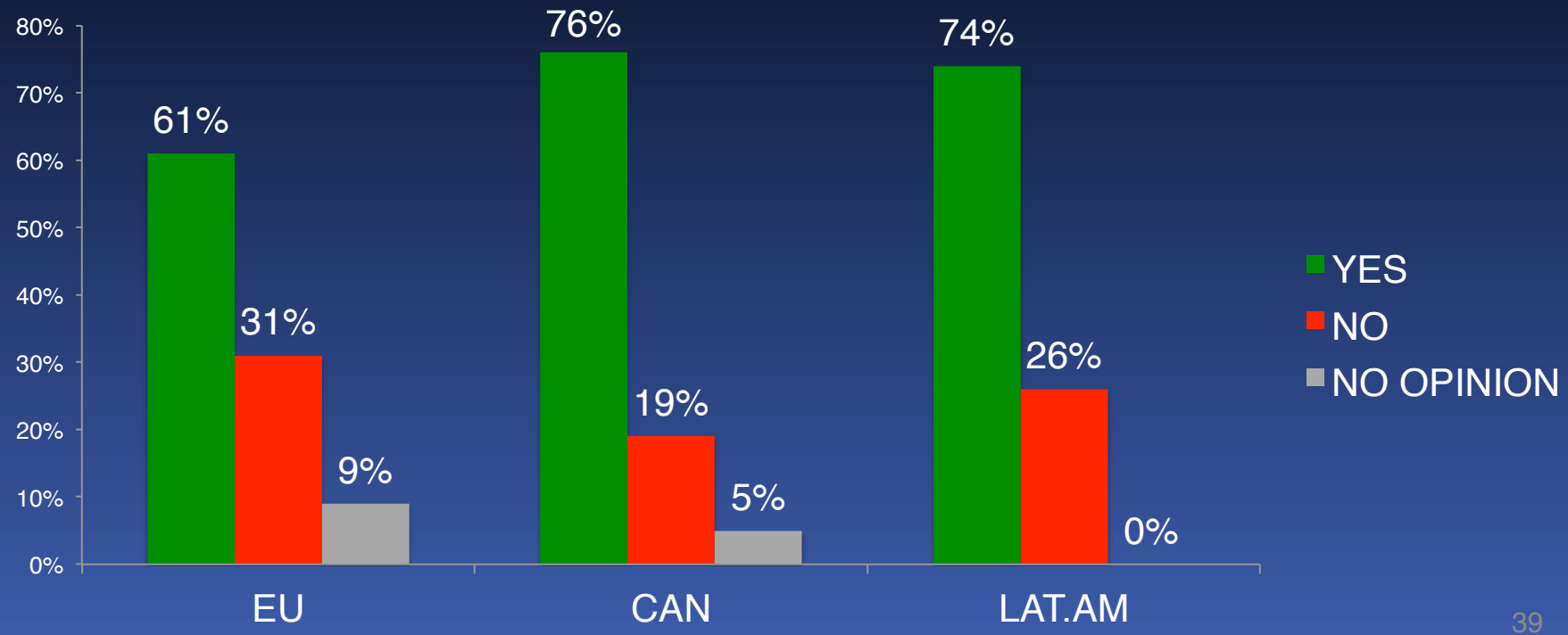
ASBM Physician Surveys Show Potential for Confusion in Absence of Distinguishable Names

"Is a Biosimilar With The Same Non-Proprietary Name STRUCTURALLY IDENTICAL to its Reference Product?"



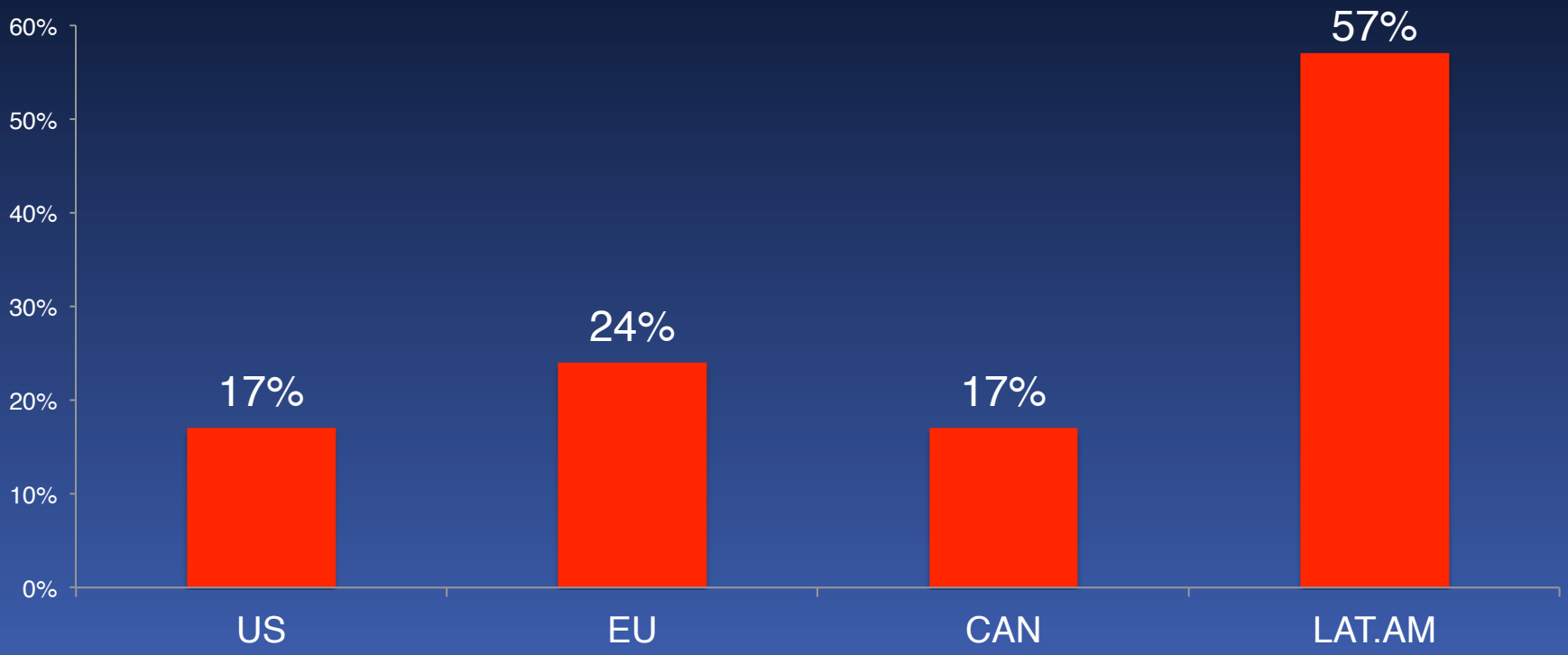
Percentage of Physicians Saying A Biosimilar Sharing an INN with its Reference Product Implies Approval for the Same Indications:

(This may or may not be the case…)



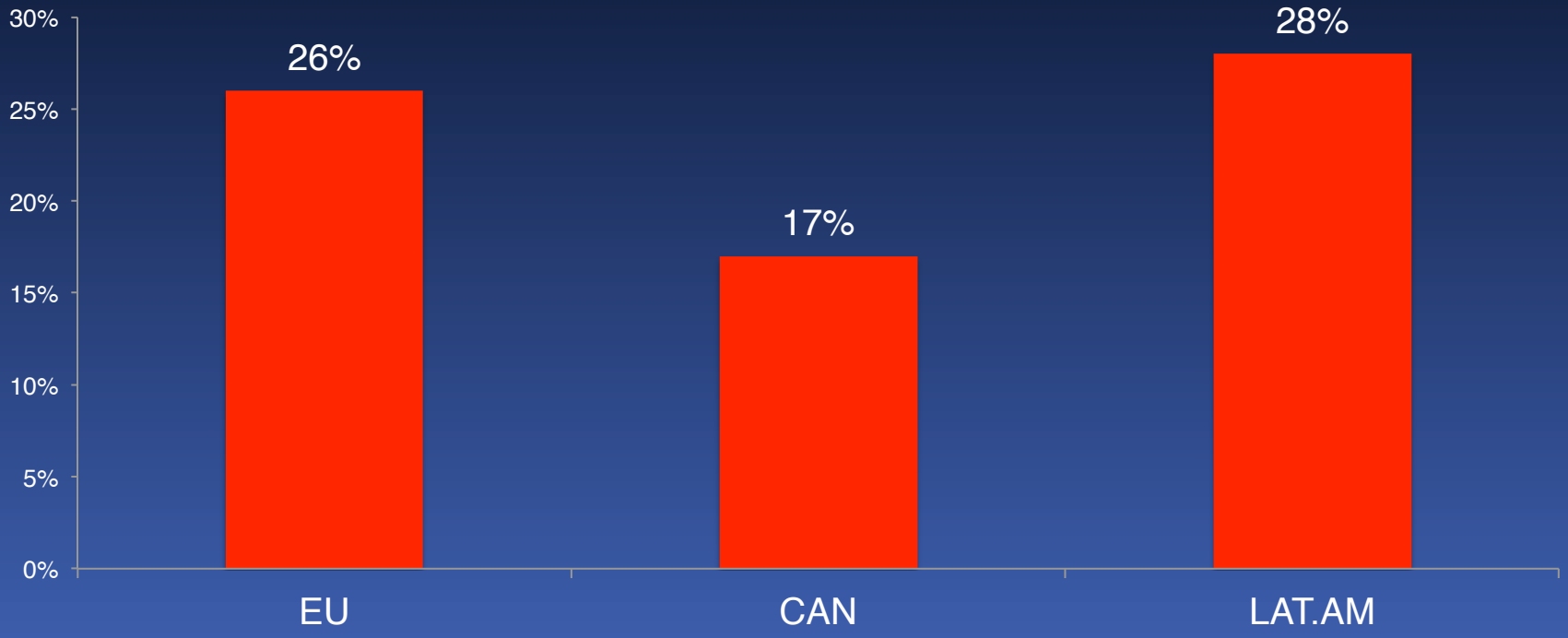
Percent of Physicians Using INN Only when Identifying Medicine in Patient Record

(This could result in patient receiving the wrong medicine.)

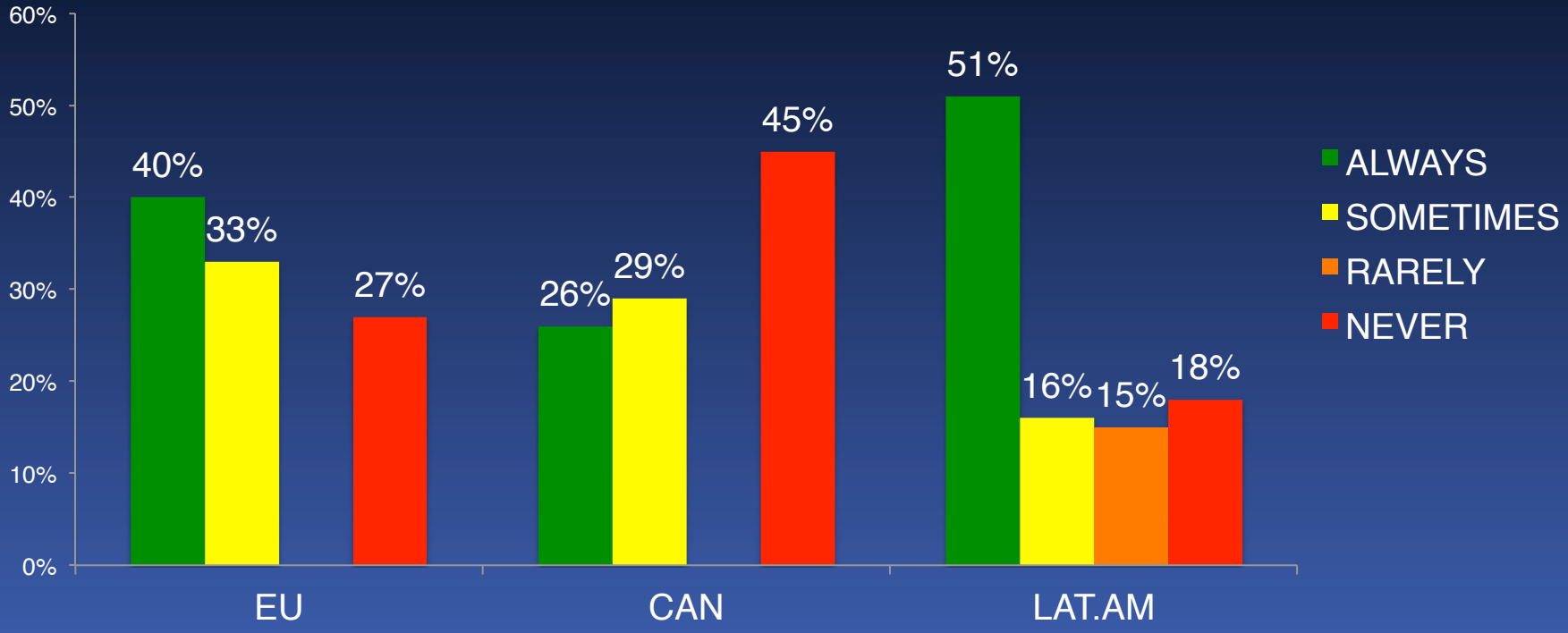


Percent of Physicians Using INN Only when Reporting Adverse Events.

(This could result in improper attribution or pooling of adverse events.)

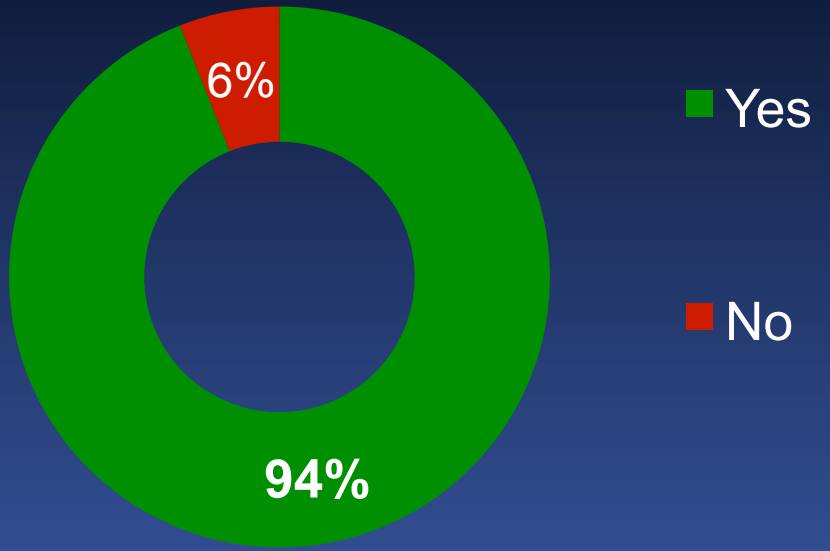


Percent of Physicians Using BATCH (LOT) NUMBER when Reporting Adverse Events.



Latin American Survey: Physicians Overwhelmingly Support WHO's Biological Qualifier

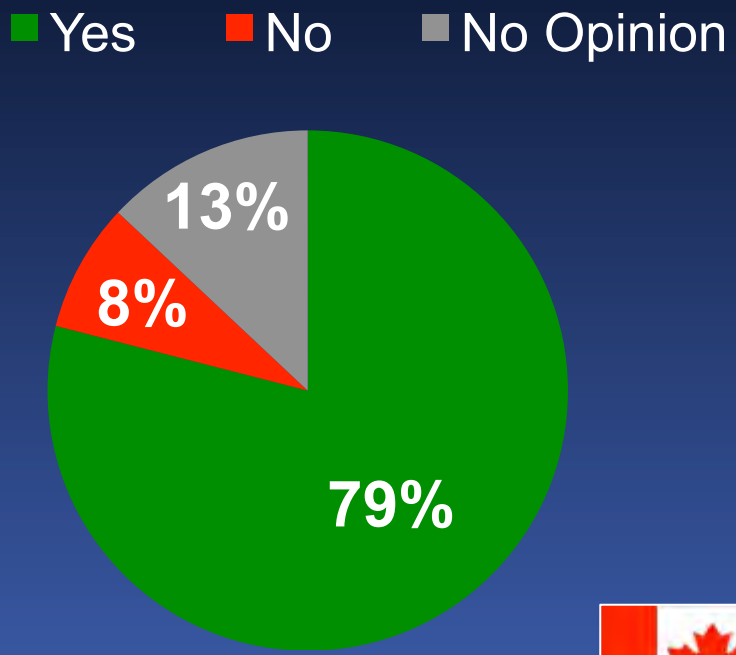
"Do you think [The WHO's proposed] "biologic qualifier" would be useful to you to help you ensure that your patients receive the right medicine that you have prescribed for them?" (N=399)



In Canada, Where Biosimilars Are in Clinical Use, Physicians Support Distinguishable Names

Health Canada / Santé Canada

"In your opinion, should Health Canada insist on a distinct non-proprietary / generic name for every biologic or SEB product approved by them?" (N=427)



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.

SOME SUGGESTED WAYS OF DISTINGUISHING BIOSIMILARS:

Unique USAN?

Same USAN + Suffix?

Same USAN + NDC Code

Prefix + Same USAN?

Distinguishable Naming: ASHP Position

- The American Society of Health-System Pharmacists (ASHP) is not opposed to the addition of a suffix, but opposes to use of prefixes, which it feels can lead to medication error.

- Breast cancer medication KADCYLA® (ado-trastuzumab) is dosed differently from its reference biologic HERCEPTIN® (trastuzumab). Cases have occurred wherein a prescribing physician has mistakenly omitted the distinguishing prefix, resulting in a patient receiving the wrong medication at the wrong dose.

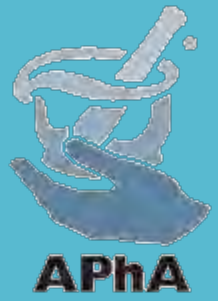
- ASHP is not opposed to adding the National Drug Code (NDC) to the USAN as a suffix, but the NDC not being used to track a product in all settings, reuse of NDCs by manufacturers, and other concerns may make this approach problematic.

"**…We do not oppose the addition of suffixes** to the INN name if experts believe this approach is needed to facilitate pharmacovigilance,"

- Christopher Topoleski, ASHP Director of Federal Regulatory Affairs.

Distinguishable Naming: APhA Position

- APhA does not support Unique nonproprietary names on the grounds that it may interfere with current pharmacy safety alert systems and complicate the collection of global safety information.
- As with Human Growth Hormone and Insulin, the same nonproprietary name will not necessarily denote interchangeability, but rather be used to categorize a similar therapeutic drug.
- APhA supports a unique identifier, such as an NDC code that pharmacies already use to track products for identifying or tracking the specific drug that a patient is prescribed.



"…**a unique identifier,** such as an NDC code that pharmacies already use to track products, can be used to track the specific drug that a patient is prescribed. We recognize that non-pharmacy dispensing settings may not currently track by NDC number. "

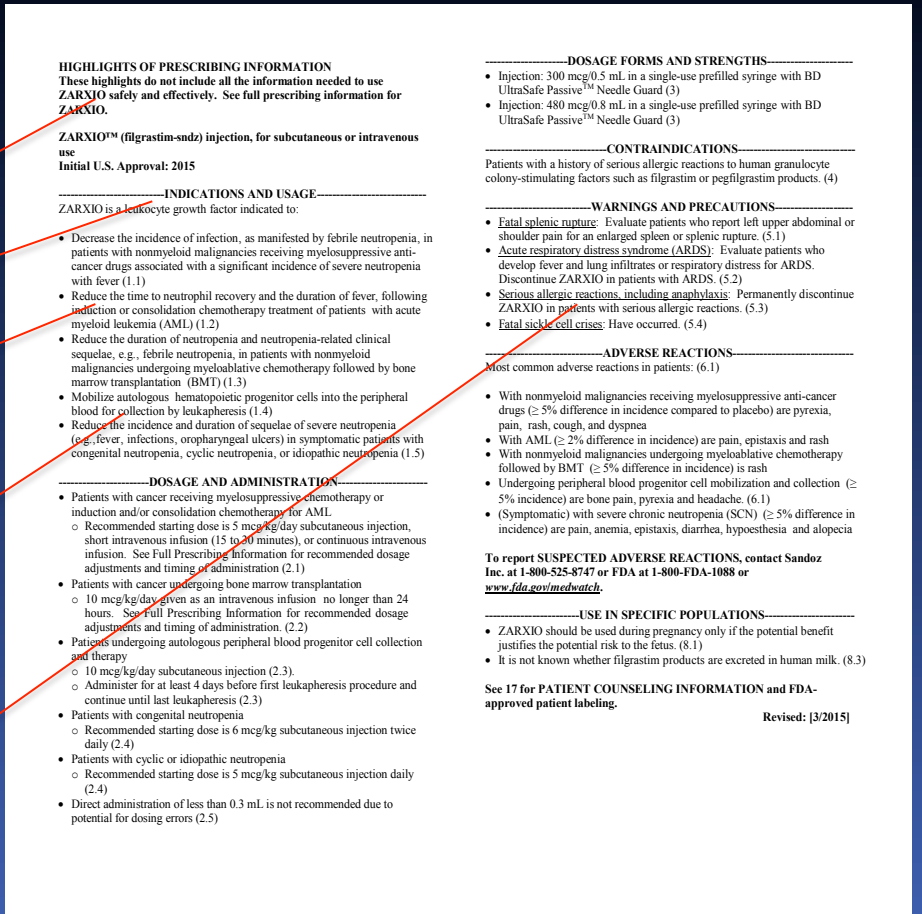
-APhA Letter to FDA, May 2012.

Biosimilar Labeling

Concerns Surrounding 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.



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- 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*.

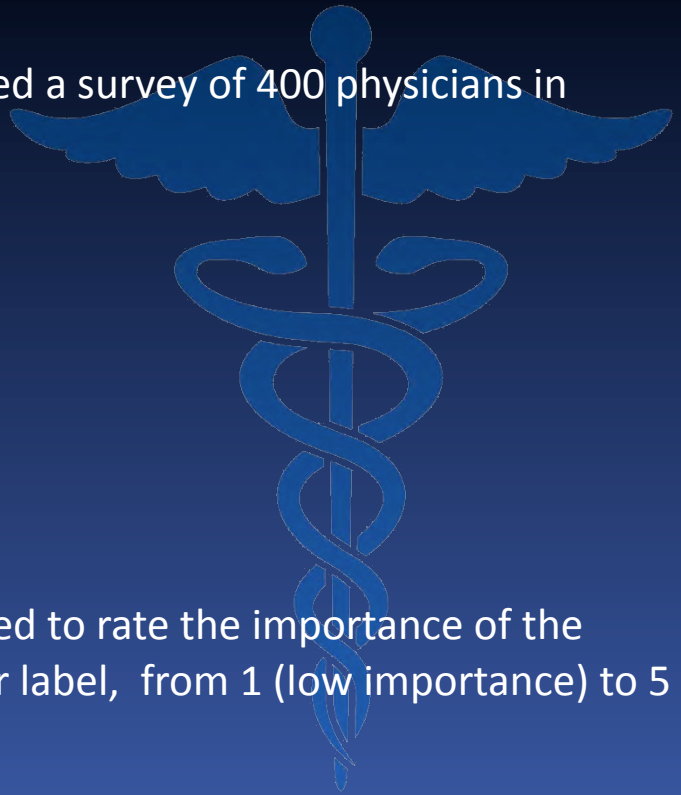
----------USE IN SPECIFIC POPULATIONS----------

- 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]

February 2015: U.S. Labeling Survey



February 2015: Prior to Zarxio approval, ASBM conducted a survey of 400 physicians in specialties in which biologics are used regularly:

- Dermatology
- Endocrinology
- Oncology
- Nephrology
- Neurology
- Rheumatology

Respondents, all of whom prescribe biologics, were asked to rate the importance of the inclusion of various types on information on a biosimilar label, from 1 (low importance) to 5 (very high importance).

So What Do Physicians Want to See on a Biosimilar Label?

These items were consistently rated a “4” or a “5”- indicating high or very high importance:

90% - That product is a biosimilar

79% - A definition of biosimilarity

82% - Analytical data used by biosimilar sponsor to demonstrate its similarity to its reference product

83% - Clinical data used to demonstrate biosimilar is highly similar to reference product

79% - Post-market surveillance data on the biosimilar

77% - Name of the biosimilar's reference product

79% - Indications for which the originator is approved, but the biosimilar is not

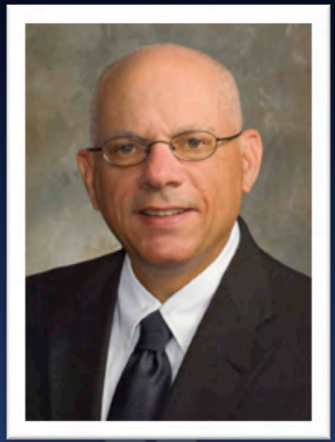
79% - Clear distinguishable reference product data from biosimilar data

79% - Clinical similarity data including immunogenicity effects

80% - Which approved indications were actually studied, vs. which were extrapolated from data in other indications?

79% - Whether or not the biosimilar is "interchangeable" with its reference product

May 2015: ASBM Letter to FDA on Labeling



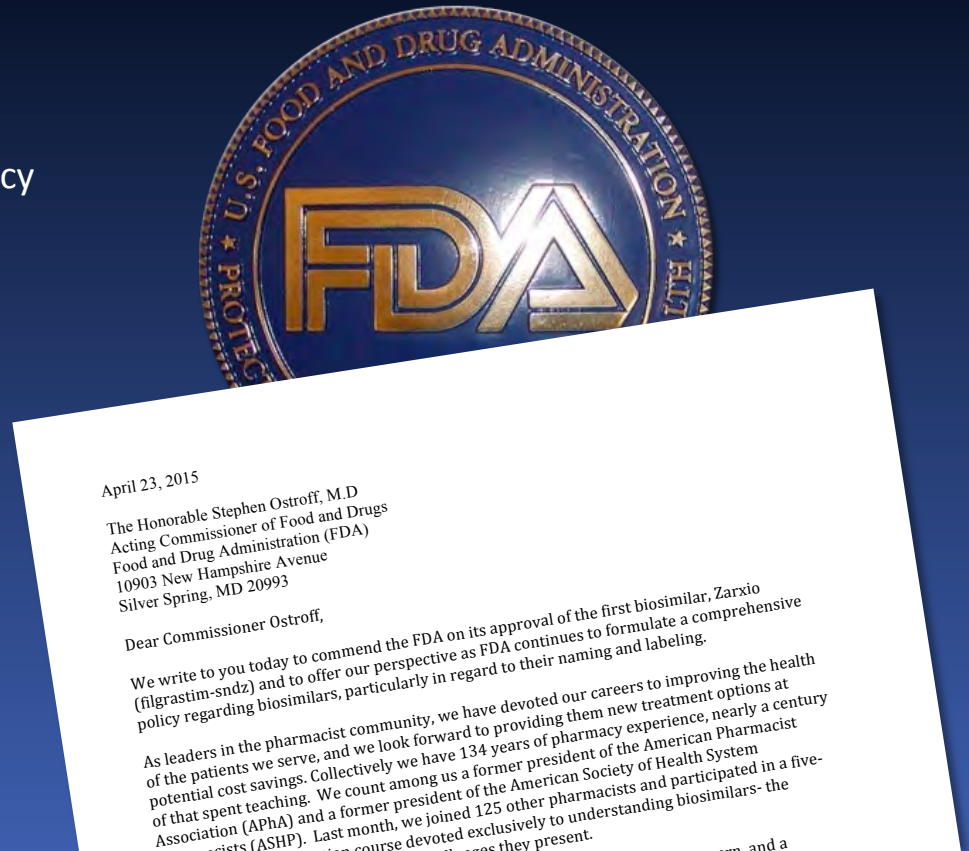
- As none of the information is on Zarxio's label, it is clear that more transparency is needed for future biosimilars.
- In May, we wrote to Acting FDA Commissioner Stephen Ostroff, MD; sharing our labeling survey results and our concerns with the lack of transparency in Zarxio's labeling.
- We commended the FDA for the distinguishable naming of Zarxio, and encouraged them to continue this practice.
- **"Physicians, like pharmacists, have a responsibility to ensure our patients receive the best information and care possible, and we simply cannot perform our duties adequately without clear, transparent naming and labeling of medications."**

Prominent Pharmacists Also Share Concerns, Write Letter to FDA on Labeling

Philip Schneider,
Professor, University of Arizona College of Pharmacy
Former President, AHSP

Ronald P. Jordan,
Dean, Chapman University School of Pharmacy
Former President, APhA

Joseph J. Bova,
Director of Continuing Education,
Long Island University College of Pharmacy



Biosimilar Substitution

Perspectives on Biosimilar Substitution in Europe and Canada

- The European Medicines Agency advises that **the physician should be in charge of the decision to switch** between the reference and biosimilar, or vice versa[1].
- "Health Canada **does not support automatic substitution** of a Subsequent Entry Biologic for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange."[2]

1 European Medicines Agency. Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products). London: European Medicines Agency; 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. Accessed November 6, 2012.

2 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php

Limited Pharmacy Substitution Recently Authorized (but not implemented) in France

- In 2014, France broke new ground by providing for very limited substitution
- Substitution law recognizes that biosimilars are not identical to their reference products.
- Patient must be initiating course of treatment (patients may not be switched from innovator to biosimilar, or biosimilar to innovator).
- Physician may block substitution by writing "non-substitutable" on prescription.
- Pharmacist must record substitution and inform physician.
- Implementation has stalled because they have no practical means of ensuring the patient is initiating treatment.

ansm
Agence nationale de sécurité du médicament et des produits de santé

Australia is Poised to Become the Only Advanced Nation to Allow Pharmacy-Level Substitution

- On May 26, 2015, Australian Health Minister Sussan Ley announced that Australia would allow automatic pharmacy-level substitution of a biosimilar without physician involvement.

- The practice is explicitly banned in many countries including the UK, Germany, Ireland, Spain, Sweden, Norway, and Finland. While France statutorily it in limited cases, this policy has never been implemented. *Only Venezuela currently permits the practice.*

- ASBM and patient groups sent letters raising patient safety concerns to the Australian government, including members of the relevant Senate Committee in advance of its hearing on the matter. The move was also opposed by the Australian Rheumatology Association.

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

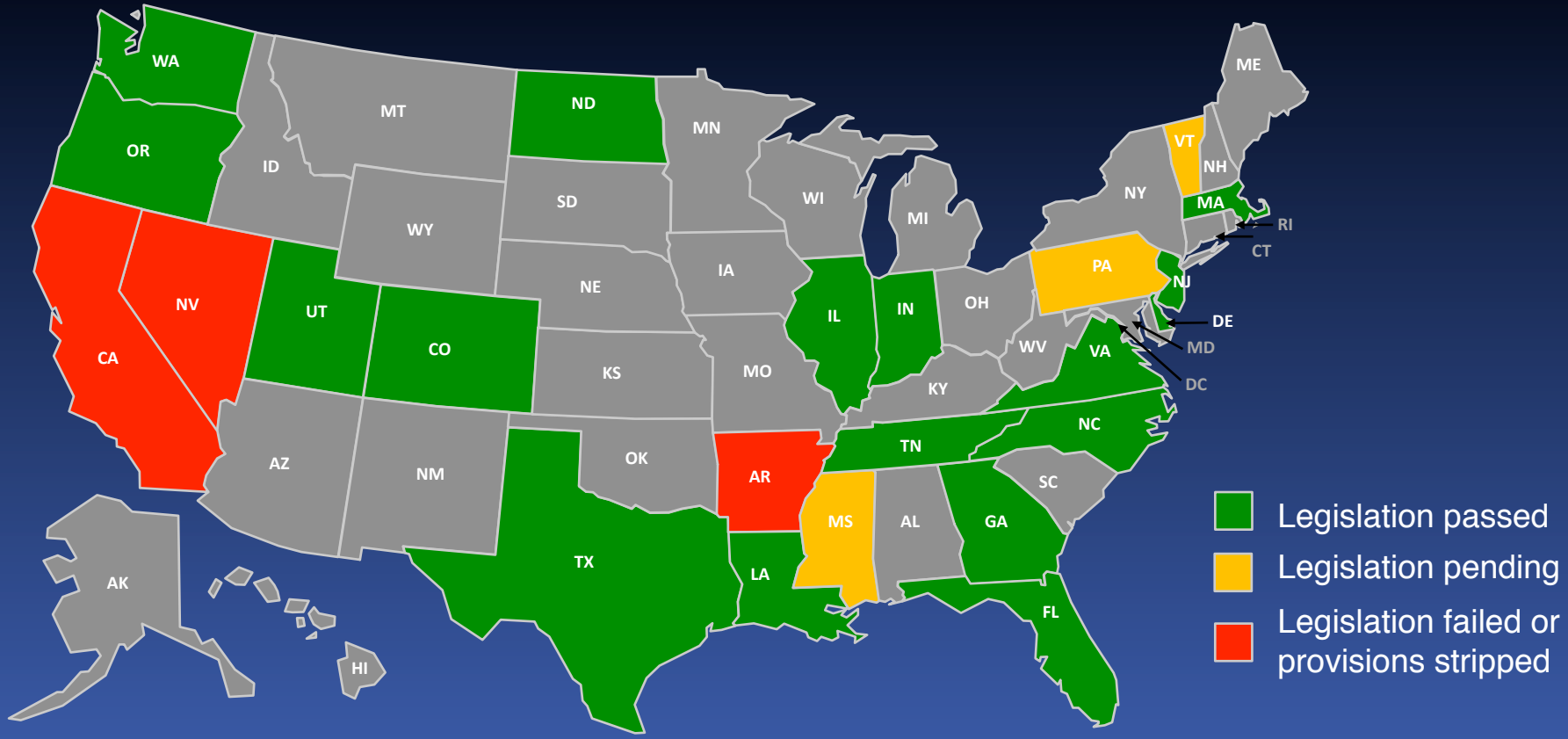
Issues Surrounding U.S. Biosimilar Substitution

- Under what circumstances may a pharmacist substitute a biosimilar (approved by FDA as interchangeable) without the involvement of the physician
- What communication is required between pharmacist and:
  - Physician
  - Patient
- What records must be kept of the substitution?
- This is the purview of state government: Legislatures, Boards of Pharmacy

Why are these Issues Important?

- Patient always needs to be informed about the medicine he/she is receiving in order to make informed choices and be an effective partner in care.
- Physician needs to be aware of what medicine patient is receiving to provide proper care.
- Accurate patient record must be kept for pharmacovigilance/post-market monitoring for adverse events and efficacy
- Physicians and pharmacists have a responsibility to the patient and to the larger community (other healthcare providers, regulators, manufacturers) to work collaboratively together – that includes **clear, timely communication.**

Physician-Pharmacist Communication Requirements by State



Communication/Record Keeping Requirements are Gaining Momentum Nationally…

- In 2014, INDIANA, DELAWARE, and MASSACHUSETTS passed bills with these requirements.
- In 2015, COLORADO, GEORGIA, ILLINOIS, LOUISIANA, NEW JERSEY, NORTH CAROLINA, TENNESSEE, TEXAS, and WASHINGTON joined them.
- New Jersey and Illinois both passed these bills unanimously and have been sent to their governors. Signature is expected shortly in Illinois.
- Similar bills being debated in CALIFORNIA, NEW JERSEY, and other states.

Biosimilar Substitution in Oregon

In 2013, Oregon led nationally on this issue by passing SB 460:

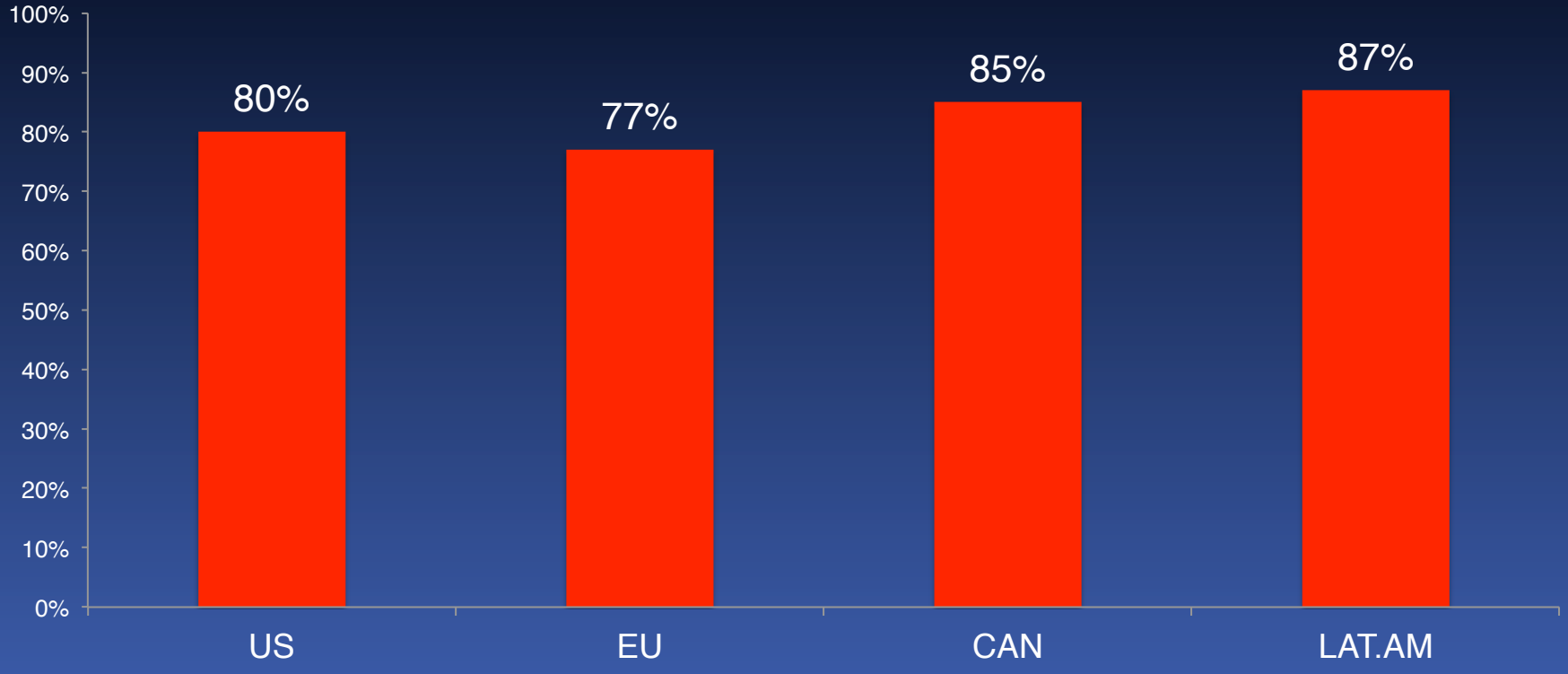
- Only biosimilars determined by FDA as “interchangeable” may ever be substituted.
- Physician may prohibit substitution.
- Pharmacist has 3 business days to notify physician of a substitution.
- Pharmacist must inform patient of substitution.
- Records of a substitution must be kept for 3 years.
- **NOTIFICATION PROVISION SUNSETS January 1, 2016**

U.S. Prescriber Survey: Physician Attitudes on Substitution

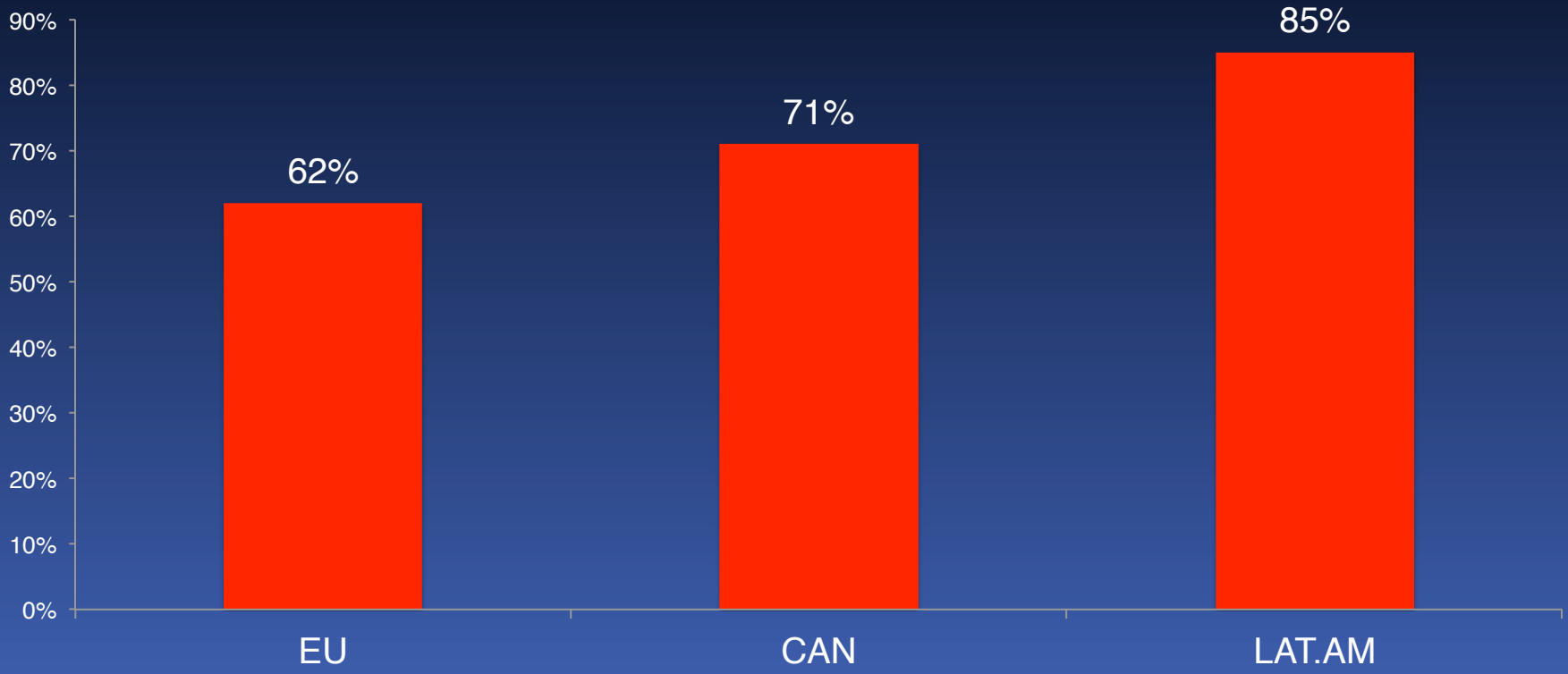
- **80%** of respondents felt NOTIFICATION after a substitution occurs was “very important” or “critical”.

- **82%** felt the authority to write “DISPENSE AS WRITTEN” was “very important” or “critical”.

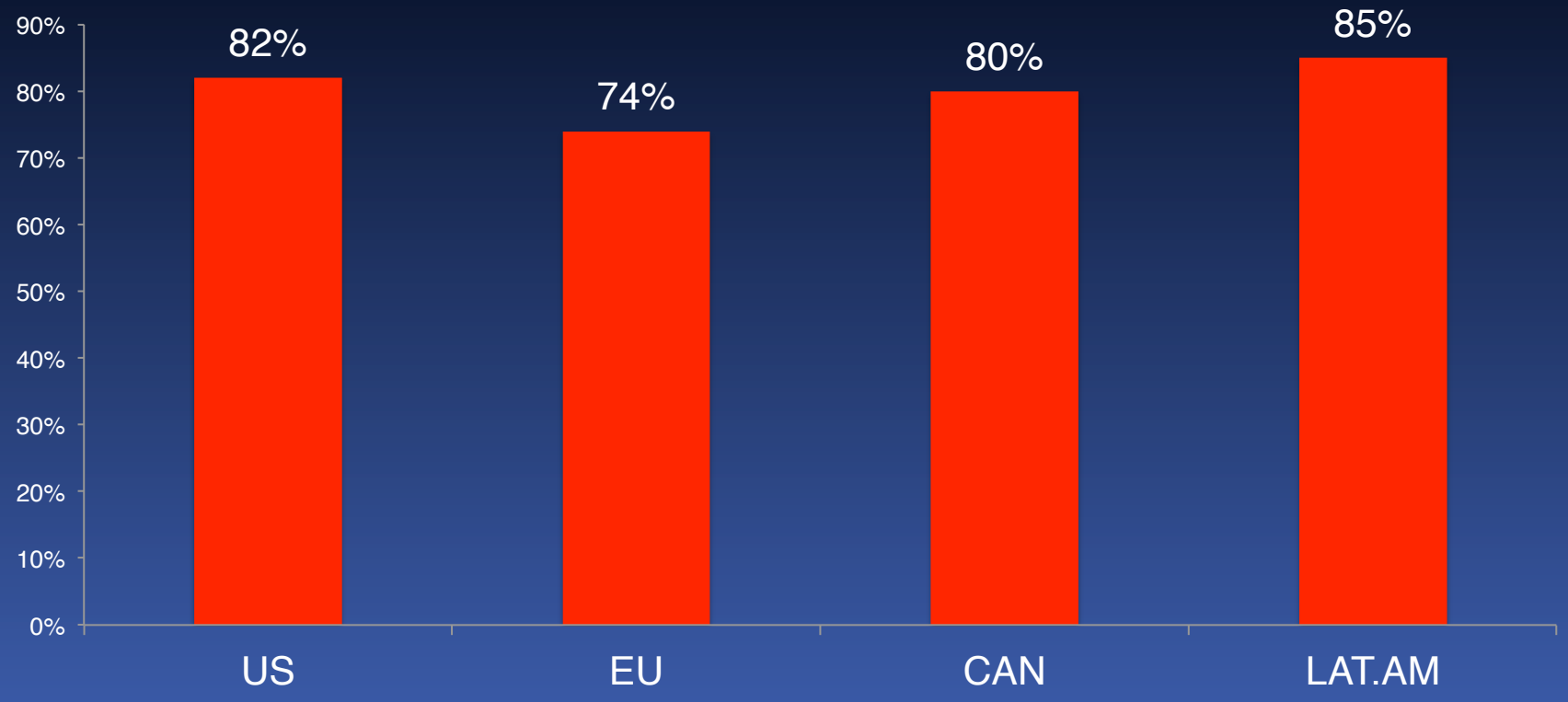
Percentage of Physicians saying NOTIFICATION in the case of a biosimilar substitution is "Very Important or Critical"



Percentage of Physicians who consider a pharmacist determination of which biologic their patient receives at initiation of treatment "unacceptable":



Percentage of Physicians saying "Dispense as Written" (DAW) Authority is "Very Important or Critical"



Physician Concern: Interchangeability and Immune Response

- Interchangeability designation means a patient can be switched back and forth between a biosimilar and its reference biologic without additional risks.
- Interchanging/Substituting medications creates numerous real and potential issues.
- We already know that there is significant variations in response to medications in the same class due to differences in chemistry of both the medications and individual.

Collaboration among Pharmacists, Physicians, Manufacturers on substitution bills has resulted in improved legislation

2013 Bill Language		2014/2015 Bill Language
"Notification"	→	**"Communication"**
Notification **only if biosimilar substituted biosimilar**	→	Communication of which biologic was was dispensed- **innovator /**
72 hours to notify	→	**10 days** to communicate
Must retain records for **5 years**	→	Must retain records for **2 years**

Physician/Pharmacist Collaboration is Key

- Physicians have the authority to specify **"do not substitute"** for biological products and that specification overrides any policy – e.g. by payers or state law – that would have substitution be the standard or default practice.

- Physicians and pharmacists should **work collaboratively** to ensure that the treating physician is aware of the exact biologic – by manufacturer – given to a patient in order to facilitate patient care and accurate attribution of any adverse events that may occurs.

SafeBiologics

ALLIANCE *for* SAFE BIOLOGIC MEDICINES

Thank You For Your Attention

michael@safebiologics.org