Biosimilars

Overview and Clinical Perspectives on Naming and Substitution

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September 26, 2018

Introduction

Philip Schneider, MS, FASHP, FFIP

- Vice President, International Pharmaceutical Federation (FIP)
- Recently retired as Professor/Associate Dean, University of AZ College of Pharmacy
- Past-President, American Society of Health-system Pharmacists
- Advisory Board Chair, Alliance for Safe Biologic Medicines

Biosimilars Pop Quiz

How familiar are you with BIOLOGIC medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How familiar are you with BIOSIMILAR medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How many biosimilars been approved by the FDA for use in the U.S.?

1. None
2. ~4
3. ~12
4. ~30

“Biosimilars are structurally identical to the reference biologic product upon which they are based.”

1. TRUE
2. FALSE

“In the U.S., biosimilars share the same non-proprietary name as their reference product, as with generics.”

1. TRUE
2. FALSE
3. NOT SURE

“A biosimilar is by definition interchangeable with its reference biologic product.”

1. TRUE
2. FALSE
3. NOT SURE

“A pharmacist can substitute any FDA-approved biosimilar in place of the prescribed originator biologic”

1. TRUE
2. FALSE

“As a pharmacist, I believe I will have a role in making decisions about the choice of biologics for specific indications.”

1. YES
2. NO
3. NOT SURE

“I believe the safe use of biosimilars will reduce healthcare costs.”

1. YES
2. NO
3. NOT SURE

Which of the following tools will you use to realize the potential cost benefits of biosimilars:

1. The formulary system
2. Clinical practice guidelines that specify the choice of drugs
3. Therapeutic interchange policy
4. Patient-specific dialog with the prescriber on a case-by-case basis
5. All of the above

“I need and plan to learn more about biologics to prepare myself for a role in the safe use of biosimilars.”

1. TRUE
2. FALSE

Biologics and Biosimilars: Overview

How Do Biologics Differ From Chemical Medicines?

Differences Between Biologic and Chemical Medicines

- **SIZE: Chemical compounds are generally much smaller in size than biologics and are generally unseen by the human immune system.**

- **STRUCTURE:** The structure and function of a chemical compound are simple and straightforward, but **a biologic protein has a complex three-dimensional structure.** Some of the proteins have post-translational modifications in the form of sugar attachments (called glycosylation) at specific sites, or they may have chemical modifications. Due to the structural complexity of biologics, the relationship between structure and function is often unclear (as explained on the subsequent slide under characterization).

Differences Between Biologic and Chemical Medicines
(Continued)

- **STABILITY:** Chemical drug structure is defined by rigid and stable covalent bonds, whereas a protein's structure is defined by the sequence (relatively stable covalent bonds) AND the three-dimensional folding into a structure stabilized by weak non-covalent bonds. The interactions of many weak bonds give proteins a three-dimensional structure and functional flexibility but also make it **sensitive to chemical and physical degradation.**

- **VARIABILITY:** While an active pharmaceutical ingredient of a drug consists of a single, well-defined structure, a biologic medicine exhibits a diversity of structures due to being prone to weak non-covalent bonds as well as the diversity of enzymatic and chemical modifications that can occur. **Consequently, a biologic medicine is a heterogeneous mixture of product and its related components as well as impurities from the manufacturing process.**

Differences Between Biologic and Chemical Medicines
(Continued)

- **MANUFACTURING:** Chemical compounds are manufactured using chemical reactions that are predictable and robustly reproducible, so an identical copy can be made. However, biotechnology medicines are made using living cells. **Therefore, an identical copy of a biologic medicine using a different cell line and/or different manufacturing process is not possible.**

- **CHARACTERIZATION:** Chemical compounds are easy to fully characterize. In addition, since the structure of the active ingredient in the chemical drug is precisely known, we can expect to see the same pharmaceutical function in vivo.

Differences Between Biologic and Chemical Medicines
(Continued)

- **CHARACTERIZATION (continued):** Characterization of biologic medicines requires multiple, orthogonal, advanced analytical methods. **While many biologic products have been well-characterized, complete characterization to the last atom is impossible.** In addition, correlating the diverse structures in a biologic medicine to function is quite difficult.

- **IMMUNOGENICITY**: Immunogenicity is the reaction of the body's immune system to a foreign substance. Chemical compounds have a lower potential while **biologics have higher potential for immunogenicity.**

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

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"

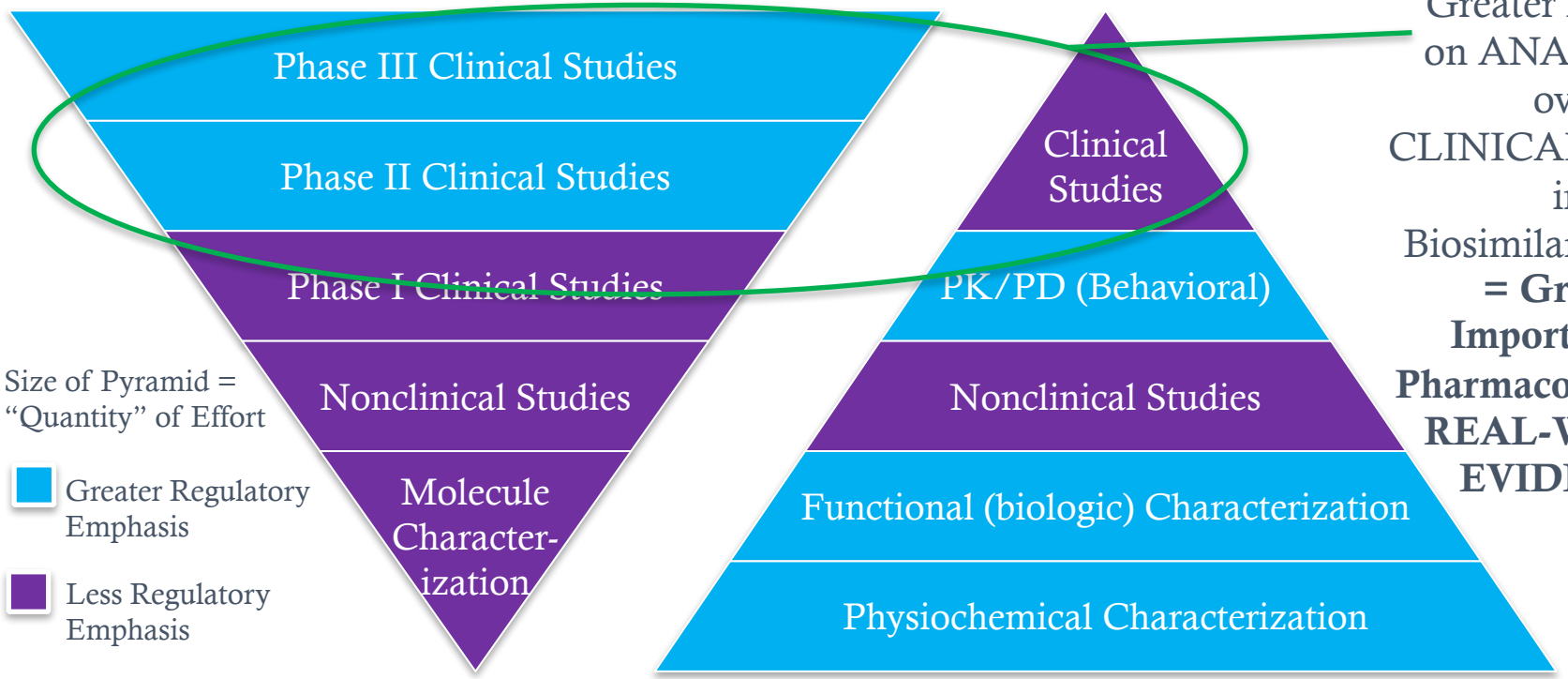
-Dr. Janet Woodcock,
Director of the Center for Drug Evaluation and Research (CDER), FDA
February 4, 2016

Potential for Immunogenicity is a 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.

Domains of Selecting a Medicine

Approval Pathway: Originator vs. Biosimilar



Greater Reliance on ANALYTICS over CLINICAL TRIALS in Biosimilar Pathway **= Greater Importance of Pharmacovigilance, REAL-WORLD EVIDENCE**

Biosimilar Development in the US: The "Patent Dance"

- Biologics Price Competition and Innovation Act of 2009 (BPCIA).
- Law intended to facilitate biosimilar development in the US.
- Patent provisions specify an information exchange between originator and biosimilar developer to encourage efficient resolution of patent conflicts.
- Some parties have declined to "dance"; litigation is common.
- 12 years of data exclusivity is provided for manufacturer of the originator biologic, after which biosimilar manufacturer may rely on the originator data to be approved by FDA.

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 only approved for same indications as Myozyme in 2014.

Myozyme becomes Lumizyme after biologics scale-up

By Nick Taylor, 16-Feb-2009

Related tags: Genzyme, Myozyme, FDA

Genzyme will launch the same biologic under two different names in the US after the FDA decided the drug produced at 2000L was considerably different to the 160L version.

US Food and Drug Administration (FDA) approval is now imminent, according to Genzyme, which would draw a line under a challenging 10 months for the company's Myozyme.

In an effort to scale up production of Myozyme Genzyme built a facility housing a 2000L bioreactor, which offered considerably more capacity than the 160L site.

However, the FDA ruled that in the process of scaling up from 160L to 2000L the product had changed sufficiently to require a new Biologics License Application (BLA).

Europe Leads in Biosimilar Approvals

50 biosimilars

Abasaglar insulin glargine
Abseamed epoetin alfa
Accofil filgrastim
Amgevita adalimumab
Bemfola follitropin alfa
Benepali etanercept
Binocrit epoetin alfa
~~Biograstim filgrastim~~ (withdrawn)
Blitzima rituximab
Cyltezo adalimumab
Epoetin alfa Hexal epoetin alfa
Erelzi etanercept
Filgrastim Hexal
~~Filgrastim ratiopharm~~ (withdrawn)
Flixabi infliximab
Grastofil filgrastim
Halimatoz adalimumab
Hefiya adalimumab
Herzuma trastuzumab
Hulio adalimumab
Hyrimoz adalimumab
Imraldi adalimumab
Inflectra infliximab
Inhixa enoxaparin sodium
Insulin lispro Sanofi
Kanjinti trastuzumab
Lusduna insulin glargine
Movymia teriparatide
Mvasi bevacizumab
Nivestim filgrastim
Omnitrope somatropin
Ontruzant trastuzumab
Ovaleap follitropin alfa
Pelgraz pegfilgrastim
Ratiograstim filgrastim
Remsima infliximab
Retacrit epoetin zeta
Ritemvia rituximab
Rituzena rituximab
Rixathon rituximab
Riximyo rituximab
Semglee insulin glargine
Silapo epoetin zeta
Solymbic adalimumab
Terrosa teriparatide
Tevagrastim filgrastim
Thorinane enoxaparin sodium
Trazimera trastuzumab
Truxima rituximab
Udenyca pegfilgrastim
~~Valtropin somatropin~~ (withdrawn)
Zarzio filgrastim
Zessly infliximab

http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe accessed 8/28/18

Australian Biosimilar Approvals

Australian Government
Department of Health
Therapeutic Goods Administration

16 biosimilars

Aczicrit	epoetin lambda
Amgevita	adalimumab
Basaglar	insulin glargine
Bemfola	follitropin alfa
Brenzys	etanercept
Erelzi	etanercept
Grandicrit	epoetin lambda
Inflectra#	infliximab
Nivestim#	filgrastim
Novicrit#	epoetin lambda
Omnitrope#	somatropin
Renflexis	infliximab
Riximyo	rituximab
SciTropin A	somatropin
Tevagrastim#	filgrastim
Zarzio#	filgrastim

Canadian Biosimilar Approvals

Health Canada

6 biosimilars, 1 FOB

Brenzys Etanercept

Erelzi Etanercept

Grastofil filgrastim

Inflectra infliximab

Omnitrope Somatroptin

Remsima infliximab

Lapelga pegfilgrastim

http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Canada accessed 8/28/18

Latin America Biosimilar Approvals

10 biosimilars

Etanar	etanercept
Etart	etanercept
Fiprima	filgrastim
Infinitam	etanercept
Kikuzubam	rituximab
Novex	rituximab
Reditux/ Tidecron	rituximab
Remsima	infliximab
Usmal	rituximab
Zedora	trastuzumab

http://www.gabionline.net/Biosimilars/General/Similar-biotherapeutic-products-approved-and-marketed-in-Latin-America accessed 8/28/18

Twelve Biosimilars Currently Approved in U.S.

12 biosimilars, 2 FOBs

Admelog insulin lispro*
Basaglar insulin glargine*
Epoetin Hospira epoetin alfa
Amjevita (adalimumab-atto)
Cyltezo (adalimumab-adbm)
Erelzi (etanercept-szzs)
Fulphilia (pegfilgrastim-jmdb)
Inflectra (infliximab- dyyb)
Ixifi (infliximab-qbtx)
Mvasi (bevacizumab-awwb)
Nivestym (filgrastim-aafi)
Ogivri (trastuzumab-dkst)
Renflexis (infliximab-abda)
Retacrit (epoetin alfa-epbx)
Zarxio (filgrastim-sndz)

http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-the-US accessed 8/28/18

Of the 12 Biosimilars Currently Approved in U.S., None are "Interchangeable"

Amjevita (adalimumab-atto)
Cyltezo (adalimumab-adbm)
Erelzi (etanercept-szzs)
Fulphilia (pegfilgrastim-jmdb)
Inflectra (infliximab- dyyb)
Ixifi (infliximab-qbtx)
Mvasi (bevacizumab-awwb)
Nivestym (filgrastim-aafi)
Ogivri (trastuzumab-dkst)
Renflexis (infliximab-abda)
Retacrit (epoetin alfa-epbx)
Zarxio (filgrastim-sndz)

What Does "Interchangeable" Mean?

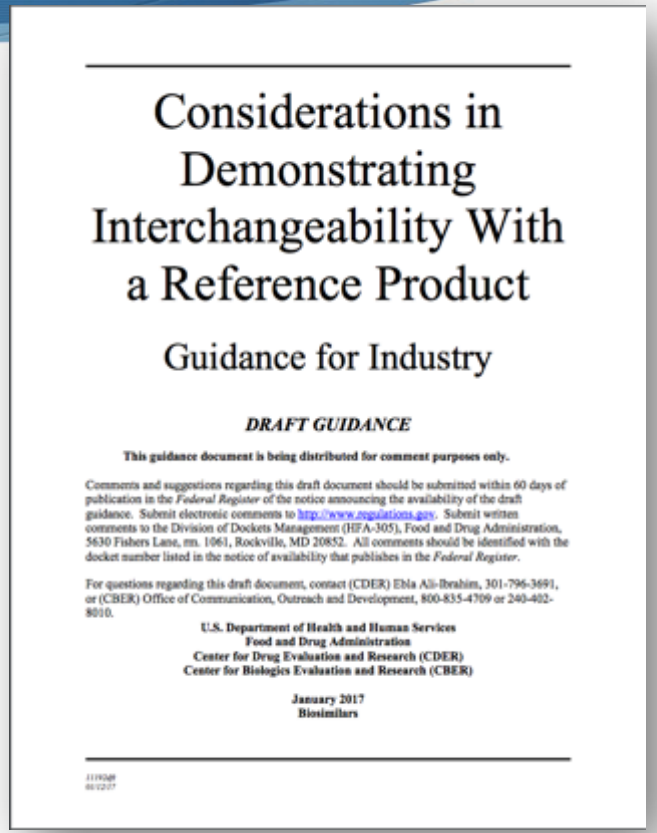
A higher regulatory standard to meet. More data is required.

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.**

FDA Draft Interchangeability Guidance

- On January 12th, 2017, FDA released its Draft Guidance on Interchangeability.



Considerations in Demonstrating Interchangeability With a Reference Product

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) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

January 2017
Biosimilars

Naming

Biologic Naming: Why It's a Key Policy Issue

How should biologics, including biosimilars, be named…

…to show that they are highly similar, but not identical?

…to differentiate biosimilar from its reference product?

…to differentiate biosimilar A from biosimilar B, C, D, etc.?

Currently this is handled on a country-by-country basis.

Biologic Naming

- Biologic medicines, like other medicines, are assigned an **International Nonproprietary Name (INN)** by the World Health Organization.
- In the US, the nonproprietary name is the "USAN" United States Adopted Name. It is often, but not always, the same as the INN.
- Since an innovator biologic and its biosimilar are different medicines, and minor differences may cause adverse effects in patients, **nonproprietary names must be distinguishable from one another.**

World Health Organization

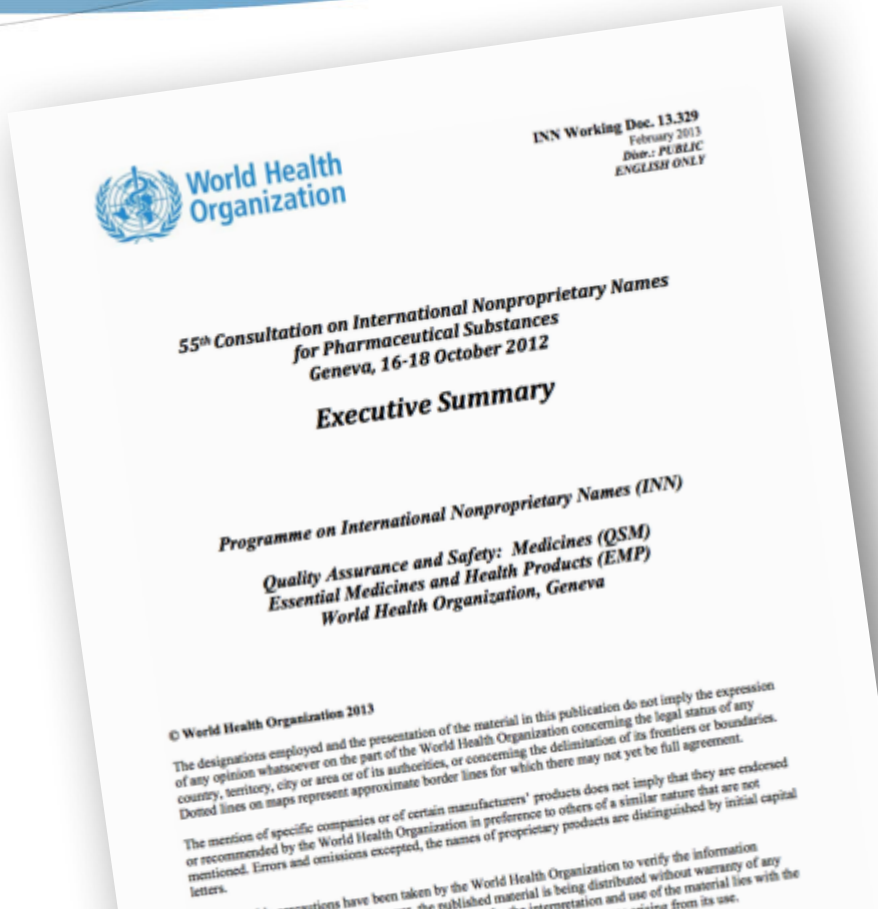
Advantages of Distinguishable Naming

- 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.

An Urgent Global Health Issue… back in 2012

"The naming of SBPs **needs to be addressed globally and soon** while the number of registered SBPs remains relatively small and with the INN programme being the best forum to achieve this."

-Executive Summary, 55th INN Consultation (October 2012) Published Feb. 2013



World Health Organization

INN Working Doc. 13.329
February 2013
Distr.: PUBLIC
ENGLISH ONLY

55th Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 16-18 October 2012

Executive Summary

Programme on International Nonproprietary Names (INN)

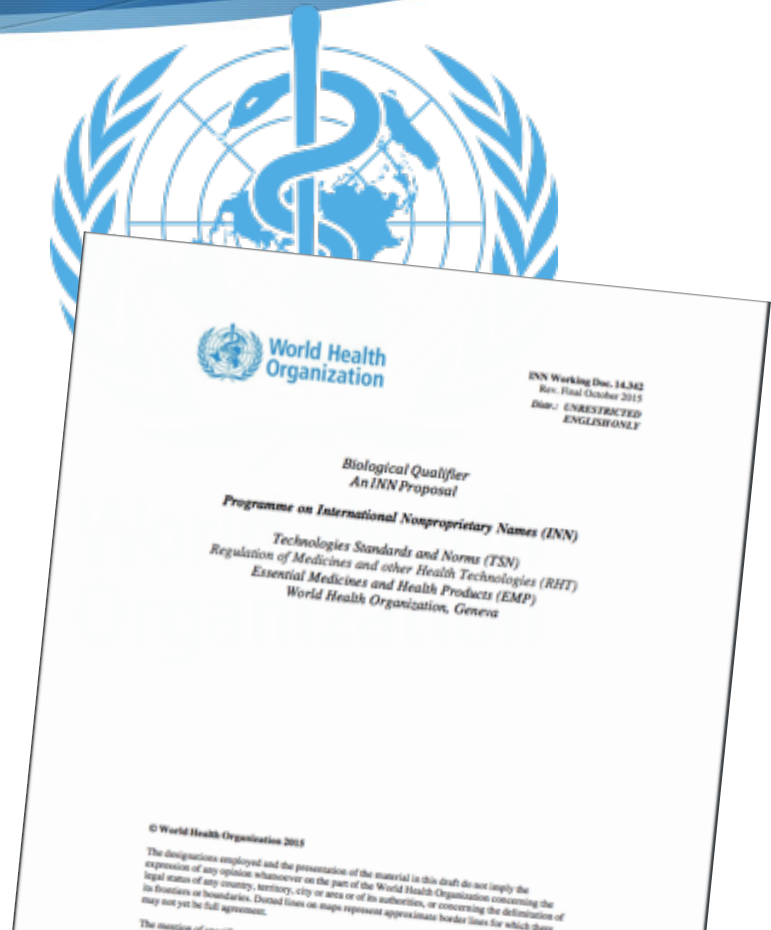
Quality Assurance and Safety: Medicines (QSM)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

ASBM Has Been Engaged on the Naming Issue Since 2013…

- Collected physician, patient, and pharmacist perspectives worldwide, including through 8 surveys of biologic prescribers in 12 countries, a national U.S. pharmacist survey, and many forums at colleges of pharmacy nationwide.
- Participated in 10 WHO INN Consultations, the most recent on May 1st of this year.
- Met with regulators worldwide to share physician survey data, most recently TGA (Feb. 2017), Health Canada (Oct 2017).

The WHO's Solution: The Biological Qualifier (BQ)

- In 2014, the World Health Organization, which assigns international nonproprietary names (INNs) proposed a distinct naming system to ensure clear product identification.
- Biologics and biosimilars would share an INN, followed by a unique four-letter suffix.
- **Yet despite broad support, this recommendation remains unimplemented.**


World Health Organization

INN Working Doc. 14.342
Rev. Final October 2015
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

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The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

WHO Meeting: April 30

- Opponents of the BQ often object to it on the grounds that it is unnecessary or redundant in countries with strong pharmacovigilance systems.
  - These reasons are typically rooted in a belief that distinct names will impede access to biosimilars- a claim that has yet to be supported with empirical evidence.

Asst. Director-General
Mariângela Simão

Head of Regulation of Medicines and other Health Technologies
Emer Cooke

INN Programme Manager
Rafaella Balocco

We believe that the opposite is true-- that the clear product identification and improved pharmacovigilance arising from distinct naming will increase confidence in biosimilars and increase their uptake.

In the absence of WHO action, regulators have been forging their own paths…

- TGA, initially supportive of WHO, has reversed itself.
- FDA has proposed and implemented its own BQ-like suffix system.
- Health Canada remains supportive of distinct names and of international harmonization. It held a stakeholder consultation and will be announcing its own naming policy later this year.

Biosimilar Naming Around the World

filgrastim-bs1
INN plus biosimilar suffix (bs1, bs2…)

filgrastim (Zarzio)
INN plus trade name

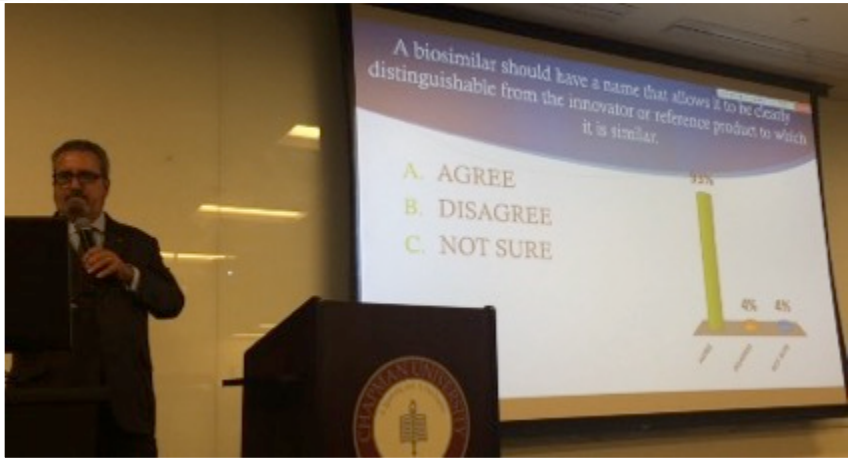
Naming System TBD,
Held Stakeholder Consultation January 2018,
willing to harmonize internationally

filgrastim-sndz
INN plus 4 letter suffix,
1st meaningful, now random

filgrasti
INN plus 4-letter suff

Pharmacists and Distinct Naming

- Pharmacists have a long history of avoiding look-alike, or sound-alike names for medicines.
- Yet a disconnect remains between practicing pharmacists and their professional associations.
- U.S. Pharmacist Associations (APhA and ASHP) have opposed distinct nonproprietary names, including the WHO and FDA proposals.
- **<u>Yet we found through our continuing education courses, that pharmacists were very supportive.</u>**



May 25, 2015
Chapman University College of Pharmacy; Irvine, CA
40 pharmacists, 93% support for distinct naming

Pharmacists and Distinguishable Naming

SOME SUGGESTED WAYS OF DISTINGUISHING BIOSIMILARS:

Unique USAN/INN?

Shared USAN/INN + Suffix?

Shared USAN/INN + NDC Code

Prefix + Shared USAN/INN?

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.

ashp
pharmacists advancing healthcare

"…**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 track the specific drug that a patient is prescribed.

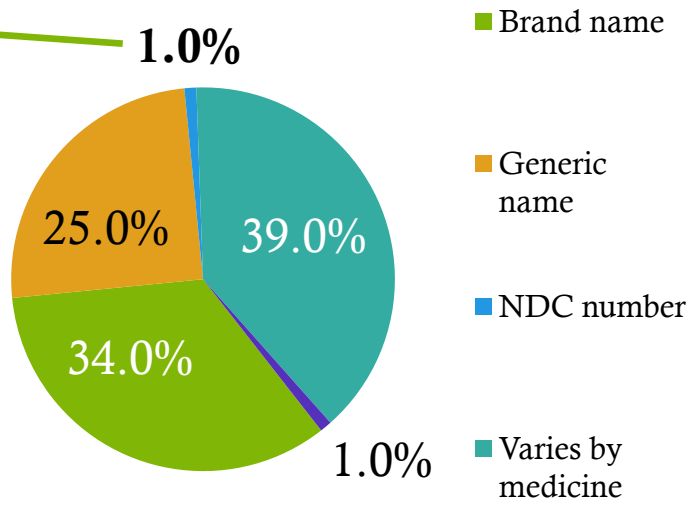
"**…a unique identifier, such as an NDC code that pharmacies already use to track products, can be used to track the specific drug that a patient is prescribed.** We recognize that non-pharmacy dispensing settings may not currently track by NDC number. "

-APhA Letter to FDA, May 2012.

Is the NDC Code an Adequate Solution?

- ASBM 2015 Survey of 400 U.S. physicians who prescribe biologics showed that NDC codes were **not used by physicians to identify in patient record (1%).**
- NDC codes are not routinely used in billing systems. Thus the identifier is missing in many circumstances where product-specific identification is important.
- Additionally, NDC code is fundamentally an attempt at **a LOCAL solution to what is essentially a GLOBAL problem.**

When you identify a medicine for prescription or recording in a patient record, are you more likely to identify the medicine by brand name, non-proprietary / generic name, or NDC number?



Distinguishable Naming: HOPA Position

- **Supports all biosimilars- interchangeable and non-interchangeable- sharing a nonproprietary name with their reference products.** Opposes FDA and WHO suffix proposals.

AMCP Academy of Managed Care Pharmacy®

"We believe that it is critically important to patients, providers, and both public and private payers that these **substantial cost savings** [of biosimilars] are not lost. By changing the established nonproprietary name of these products, these **savings are put at significant risk due to the potential for reductions in utilization."**

"**Changes will need to be made to existing software** in order to account for the addition of a suffix to INNs…These changes will add greater costs to the health care system by treating biosimilar and interchangeable biosimilar products differently from their reference products."

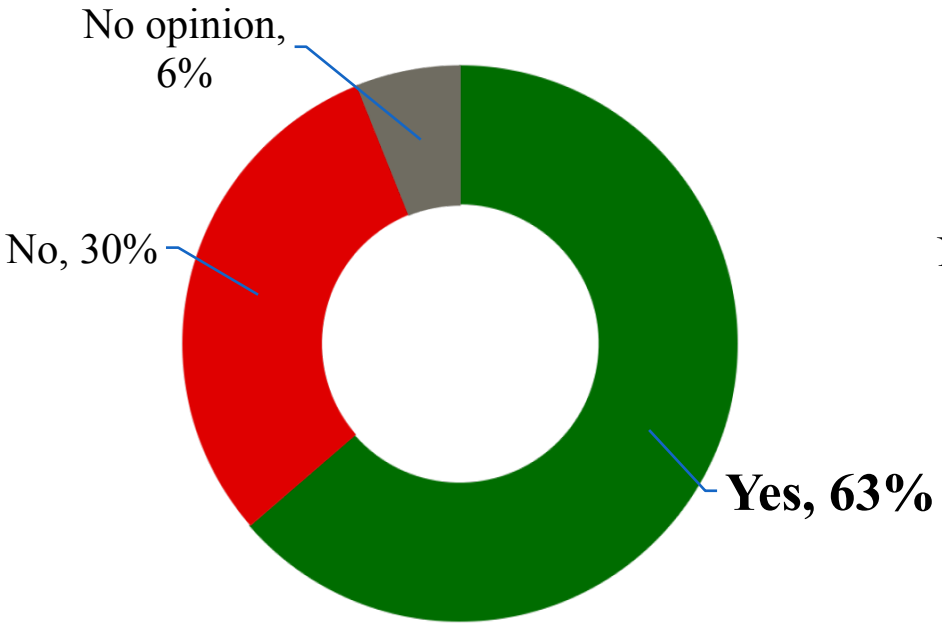
"FDA should abandon its current proposal, and instead adopt the use of standard INNs for all biosimilar and interchangeable biosimilar products."

-AMCP Comments on FDA Draft Naming Guidance, Oct. 27, 2015

ASBM 2015 U.S. Pharmacist Survey: Does a Shared INN Imply…

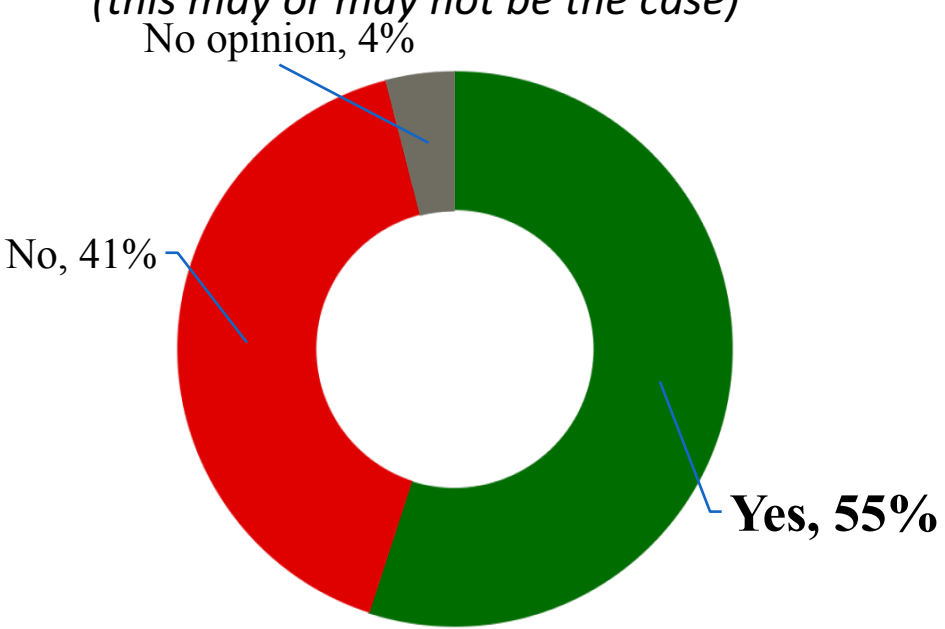
…Structural Identicality?

(this is not possible)

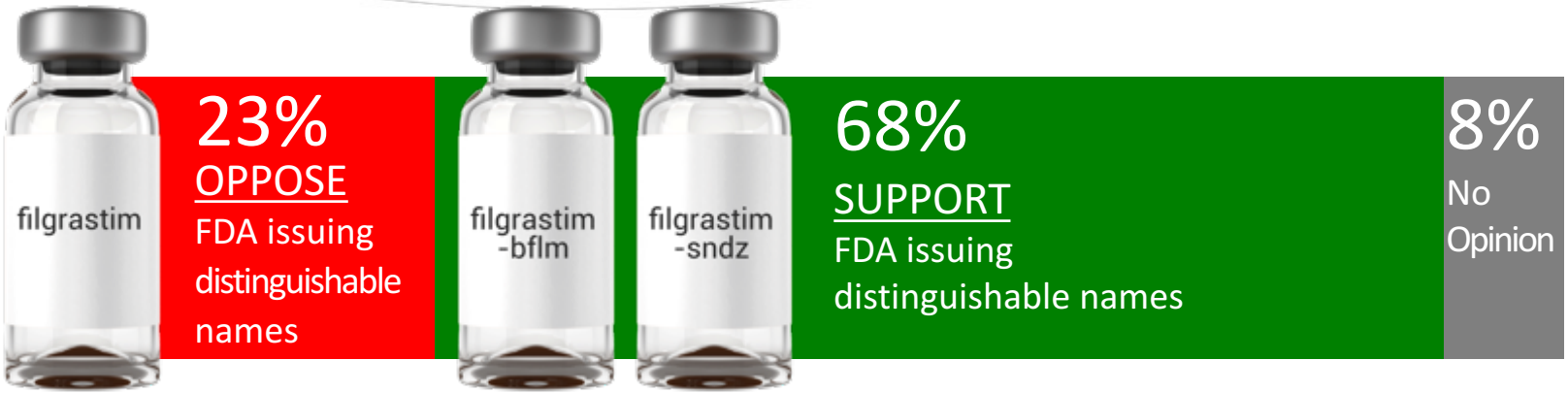


…Approval for the Same Indications?

(this may or may not be the case)



ASBM 2015 U.S. Pharmacist Survey Showed Strong Support for Distinguishable Naming



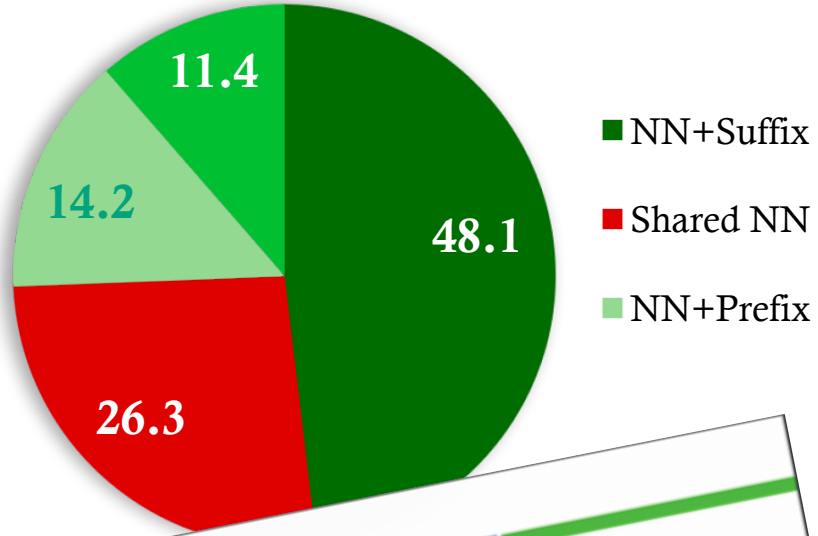
ASBM Survey of 401 U.S. Pharmacists, September 2015

2016 AMCP Study Confirmed ASBM's Results

- Published August 2016 in *Journal of Managed Care and Specialty Pharmacy, Vol. 22 (8).* Funded by Academy of Managed Care Pharmacy (AMCP); Surveyed 781 members of AMCP the and the Hematology/Oncology Pharmacy Association (HOPA)

- Again we see a disconnect between the professional organizations and the rank-and-file pharmacists… *While AMCP does not support distinct naming, their constituents do*.

- ***74% support distinct naming, 48% support distinguishing suffixes.***




RESEARCH

Biosimilar Naming Conventions: Pharmacist Perceptions and Impact on Confidence in Dispensing Biologics

Daniel Tomaszewski, PharmD, PhD

What is already known about this subject

Distinguishable Naming: HOPA Position

- Prefers prefix, but supports suffix.
- Wants Suffix to be meaningful/manufacturer based, not random.

Hematology/Oncology Pharmacy Association

"HOPA's preferred naming convention would include using the current nonproprietary name associated with the reference product and modifying it **with a prefix rather than a suffix.**

'firmly believe that
the 4-character suffix proposed should be meaningful and not "devoid of meaning" for biosimilars that are not interchangeable…In theory and lacking interchangeability guidance, HOPA's position is that interchangeable products do not have to be differentiated with a suffix."

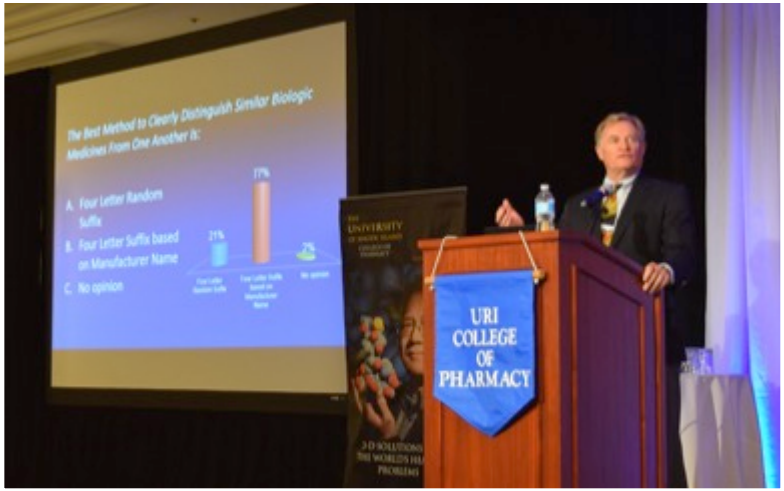
"For safety/medication error concerns as well as pharmacovigilance, this approach would make it much easier to differentiate between the biosimilar and the innovator."

-HOPA Comments on FDA Draft Naming Guidance, Oct. 27, 2015

2015 U.S. Pharmacist Survey Also Found Strong Support for Manufacturer-based suffixes.

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

Anecdotal Preference: Meaningful vs. Random Suffixes?



Newport, RI March 31st 2016
University or Rhode Island College of Pharmacy
n=150
77% support meaningful suffixes, 21% random.

Philadelphia, PA September 14th 2016
University of the Sciences, College of Pharmacy
n=50
One hand goes up in support of random suffixes.

Broad Support for Distinct Naming Among Physicians Globally

68% *of Canadian physicians support Health Canada issuing distinct names. (2017)*

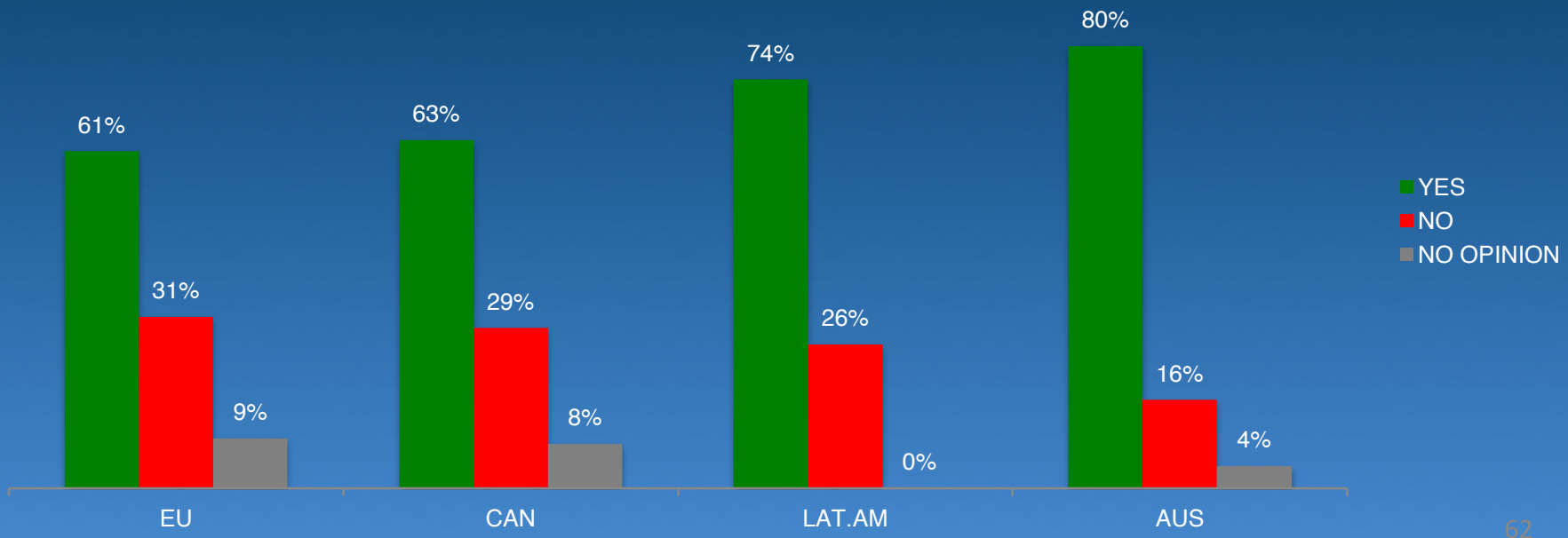
94% *of Latin American Physicians consider WHO's BQ Proposal to be "useful" in helping patients receive the correct medicine. (2015)*

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

76% *of Australian physicians support TGA issuing distinct names (2016)*

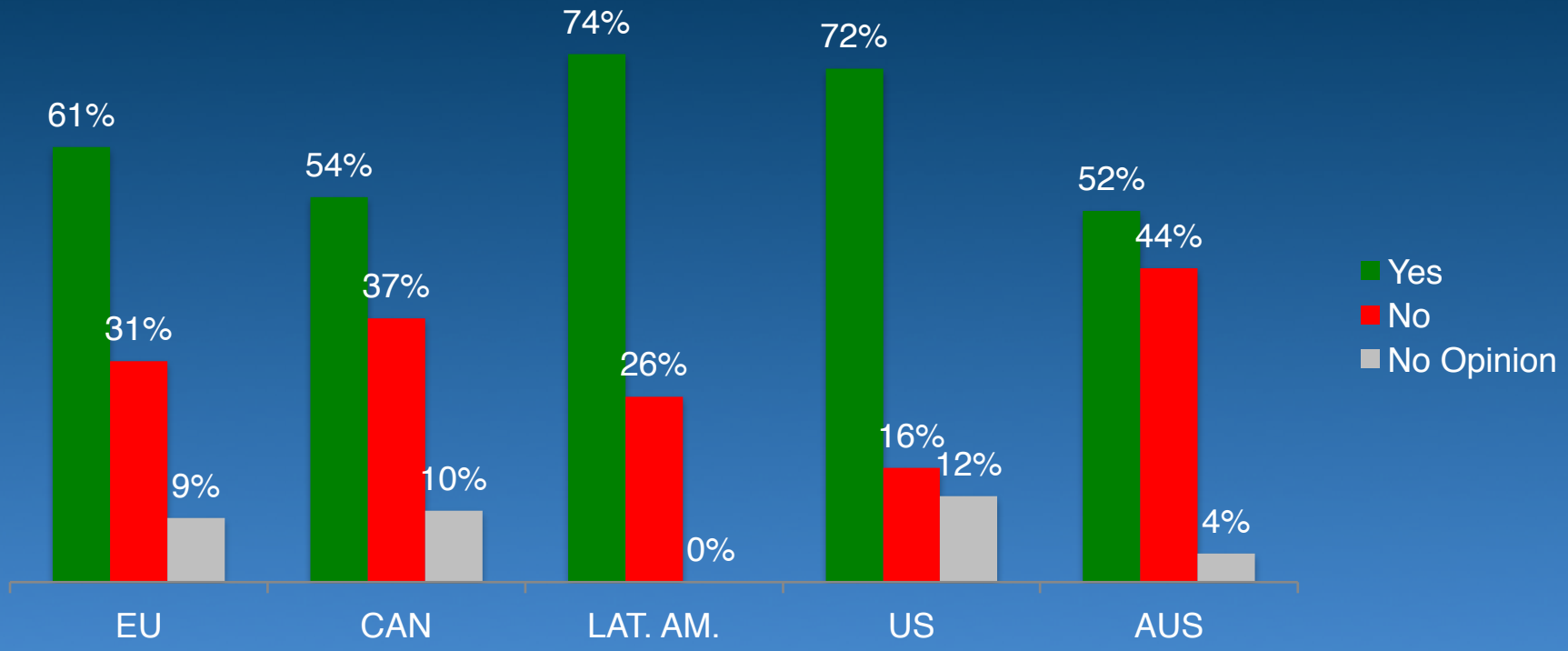
Percentage of Physicians Saying A Biosimilar Sharing an INN with its Reference Product Implies Approval for the Same Indications:

(This may or may not be the case…)



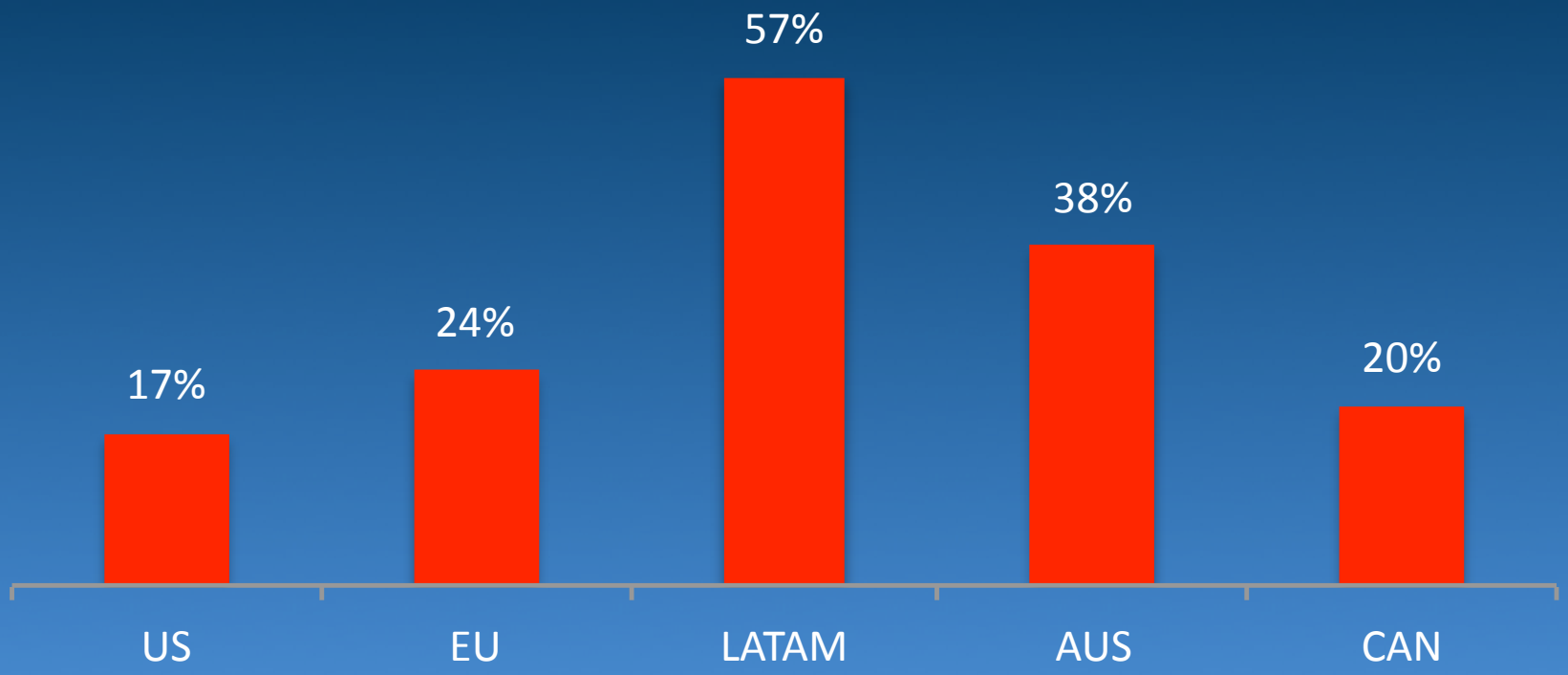
Does Same INN Suggest or Imply Structurally Identical?

(This is not the case, currently impossible)



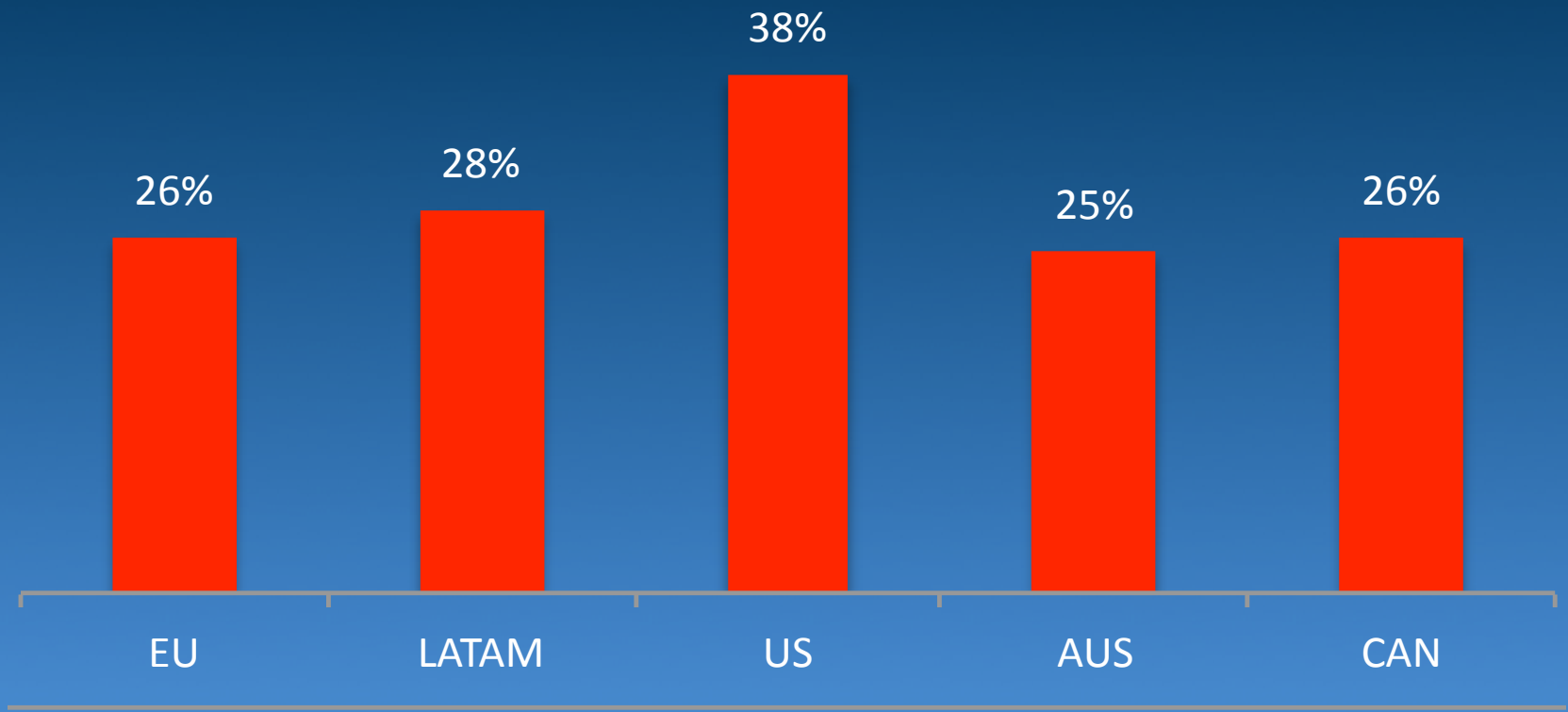
Percent of Physicians Using Only INN when Identifying Medicine in Patient Record

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



Percent of Physicians Using Only INN when Reporting Adverse Events.

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



International Harmonization Efforts

Is Suffix Implementation Feasible? **SuffixAudit**

- A web-based method of pre-defining compliance for FDA or BQ suffixes.
- Minimizes effort demanded of both the biosimilar manufacturers and regulators.
- Establishes a reliable way of avoiding conflicts beyond the stated definition of BQ or FDA suffix compliance.
- Can remain compliant with future rules and source conflicts updates.

SuffixAudit Features

- Tests proposed suffix for compatibility with FDA Naming Guidance, WHO BQ Rules, or both.
- Detects conflicts such as duplicate suffixes, incompatible combinations, or high similarity to words, stock symbols, medical terminology, etc.
- Adds new and expanded word lists (“lexicons”) including US patents and trademarks from USPTO.
- ASBM has shared with WHO and other regulatorsas one potential implementation of a harmonized international system.

ASBM Forum on International Harmonization of Biologic Nomenclature- April 11, 2018

PARTICIPANTS INCLUDED:

- *National Regulators*
- *Physician Associations*
- *Pharmacist Groups*
- *Patient Advocacy Organizations*
- *Former Regulators*
- *Biotechnology Journals*
- *Media*

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada

AAD AMERICAN ACADEMY of DERMATOLOGY | ASSOCIATION

American Gastroenterological Association

CSRO Coalition of State Rheumatology Organizations

Global Colon Cancer Association

SafeBiologics ALLIANCE for SAFE BIOLOGIC MEDICINES

CAPA Canadian Arthritis Patient Alliance experience · perspective · voice

International Alliance of Patients' Organizations A global voice for patients

Arthritis Foundation℠

SCIENTIFIC AMERICAN

nature biotechnology

Benefits of International Harmonization

Anthony Ridgway of Health Canada noted that pharmacovigilance is a GLOBAL CONCERN, not merely a matter of ensuring safety and efficacy for one's citizens within one's own borders.

If a Canadian travels outside of North America, they should have assurances they can get the correct medicine, and that robust and appropriate pharmacovigilance is present.

Benefits of International Harmonization

Mr. Ridgway also observed that a further benefit of a INTERNATIONAL NAMING SYSTEM vs. country-specific naming systems is the tremendous value of tracking the use of biosimilars in large populations across many countries.

July 12 Roundtable Discussion, Washington DC

- Follow-up discussion to April 11
- New participants included:
  - WHO INN Programme Manager Rafaella Balocco
  - APhA Chairman Thomas Menighan
- The representative from WHO
  - Heard the call for leadership in naming
  - Called out for support for their role
  - Confirmed that BQ is ”not dead”

APhA

FIP Meeting: 78th Congress of Pharmacy and Pharmaceutical Sciences (Glasgow, Scotland)

- On September 1st, WHO INN Programme Manager Dr. Rafaella Balocco and I were speakers at a symposium on biosimilars.
- Dr. Balocco also gave a presentation to College of Pharmacy Deans on The School of INN project that is intended to educate pharmacists and pharmacy students about non-proprietary names for medicines.
- There was a also presentation titled "Biosimilars and Biobetters: interchangeability issues for pharmacists, physicians and regulators" at which the speaker spoke in support of distinguishable non-proprietary names.
- Dr. Balocco was in attendance and was delighted; She shared that she is getting more positive about the future of the BQ proposal.

FIP Draft Statement of Policy: Therapeutic Interchange and Substitution

FIP STATEMENT OF POLICY

Pharmacist's authority in product selection: therapeutic interchange and substitution of pharmaceutical products

Introduction

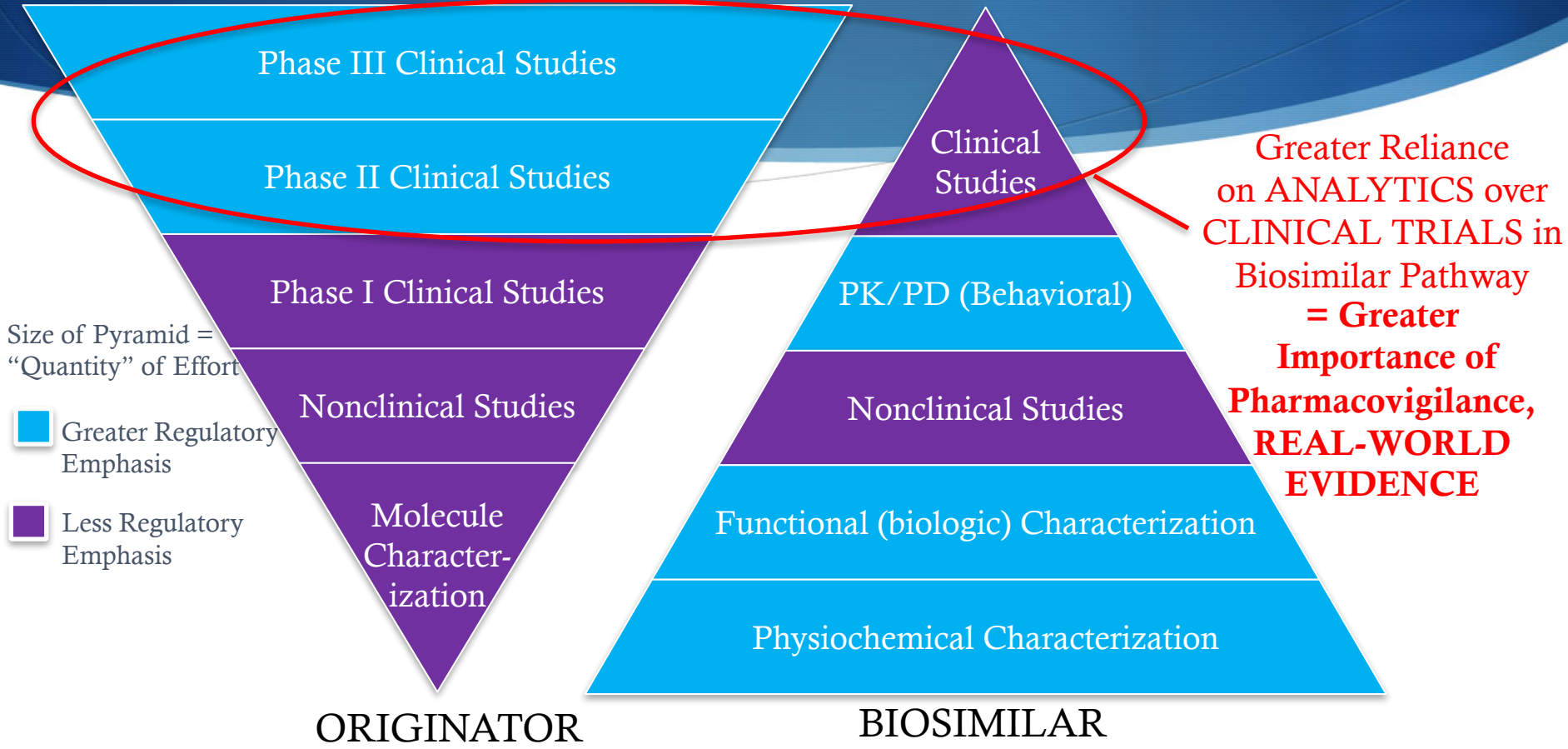
In 1992, FIP issued a statement calling on all countries to ensure the adequate quality of pharmaceutical products. Since then, countries have developed systems that guarantee that all pharmaceutical products, both manufactured locally and imported, meet satisfactory standards of quality, safety, bioavailability, bioequivalence and efficacy. As recommended by FIP at the time, governments apply the same principles for quality, safety and efficacy standards to branded and generic products.

Until recently, the marketing of some pharmaceutical products was based on the premise that the brand-name product is different from its competitors in scientifically and clinically important ways. However, it is now clear, that with appropriate exercise of medical and pharmaceutical judgement, pharmaceutical products may be interchanged according to defined criteria and the needs of the patient without compromising patient outcomes.

The WHO-FIP Joint Guidelines on Good Pharmacy Practice (2011) outline the key roles of the pharmacist. Amongst other points, it urges action by all governments, in collaboration with national pharmaceutical associations, to make full use of the expertise of the pharmacist at all levels of the health care system. It also recommends generic substitution where possible as part of the pharmacist's dispensing role.

"If appropriate, the use of international non-proprietary names (INN) for professional communications should be encouraged. **Prescribers should be recommended to use the INN** to avoid medication errors in prescribing/dispensing and to ensure patient's safety/benefits. The national legislation of the country should be taken into account. Along with the Good Pharmacy Practice principles, clarity with regard to the pharmaceutical product supplied such as tradename, batch number and expiry date should be provided by the pharmacist."

Approval Process for Biosimilars: Reduced Emphasis on Clinical Trials



Biosimilar Substitution

Background

- **Responsible use of biologic and biosimilar medicines is complicated**
  - Efficacy/effectiveness gap
  - Safety/preventable adverse drug events
  - Innovation/affordability conflicts
- **Medication-use is a team effort**
  - The greatest value from an investment in pharmacotherapy results from collaboration among health care professionals and patients
- **Accountability**
  - Health care professionals -> their patient (Regulated by the States)
  - Pharma -> innovations for patients (Regulated by the Federal Gov't)
  - Insurance companies/PBMs -> Saving money (Regulated???)

Benefits of Biosimilar Medicines

Increased treatment choices:

- Patients with conditions treated by biologics often struggle for years, trying multiple products, before becoming stable.

Cost savings:

- Unlike generics, which save 40-80%, due to higher development costs biosimilars are expected to save payers 15-30%.[1]
- A 2014 RAND Corporation study estimated 10-35% cost reduction in U.S. [2]
- In Europe, savings of between 25%-70% have been seen. [3]

1 Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4).120-6. DOI: 10.5639/gabij.2012.0103-4.036
2 https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf
3 http://www.fiercepharma.com/story/merck-discounts-remicade-uk-it-tries-fend-biosimilars/2015-10-26

Issues Surrounding 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 Concerns 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.**

EU and Canada: Oppose Automatic Substitution But Leave to Provinces/Member States

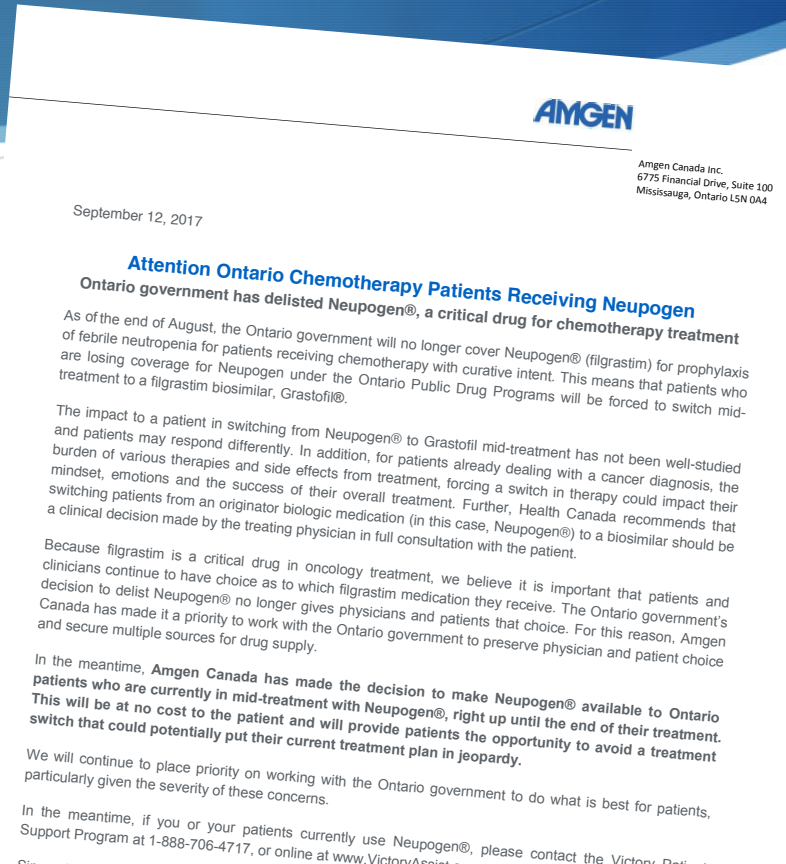
- The EMA advises that: "the physician should be in charge of the decision to switch between the reference and biosimilar, or vice versa."[1]
- "Health Canada does not support automatic substitution of a Subsequent Entry Biologic for its reference biologic drug and recommends that physicians make only 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

Ontario Delisting of Neupogen (filgrastim) 2017

"As of the end of August, the Ontario government will **no longer cover Neupogen® (filgrastim)** for prophylaxis of febrile neutropenia for patients receiving chemotherapy with curative intent. This means that patients who are losing coverage for Neupogen under the Ontario Public Drug Programs will be **forced to switch mid-treatment** to a filgrastim biosimilar, Grastofil®."



AMGEN

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, Ontario L5N 0A4

September 12, 2017

Attention Ontario Chemotherapy Patients Receiving Neupogen

Ontario government has delisted Neupogen®, a critical drug for chemotherapy treatment

As of the end of August, the Ontario government will no longer cover Neupogen® (filgrastim) for prophylaxis of febrile neutropenia for patients receiving chemotherapy with curative intent. This means that patients who are losing coverage for Neupogen under the Ontario Public Drug Programs will be forced to switch mid-treatment to a filgrastim biosimilar, Grastofil®.

The impact to a patient in switching from Neupogen® to Grastofil mid-treatment has not been well-studied and patients may respond differently. In addition, for patients already dealing with a cancer diagnosis, the burden of various therapies and side effects from treatment, forcing a switch in therapy could impact their mindset, emotions and the success of their overall treatment. Further, Health Canada recommends that switching patients from an originator biologic medication (in this case, Neupogen®) to a biosimilar should be a clinical decision made by the treating physician in full consultation with the patient.

Because filgrastim is a critical drug in oncology treatment, we believe it is important that patients and clinicians continue to have choice as to which filgrastim medication they receive. The Ontario government's decision to delist Neupogen® no longer gives physicians and patients that choice. For this reason, Amgen Canada has made it a priority to work with the Ontario government to preserve physician and patient choice and secure multiple sources for drug supply.

In the meantime, **Amgen Canada has made the decision to make Neupogen® available to Ontario patients who are currently in mid-treatment with Neupogen®, right up until the end of their treatment. This will be at no cost to the patient and will provide patients the opportunity to avoid a treatment switch that could potentially put their current treatment plan in jeopardy.**

We will continue to place priority on working with the Ontario government to do what is best for patients, particularly given the severity of these concerns.

In the meantime, if you or your patients currently use Neupogen®, please contact the Victory Patient Support Program at 1-888-706-4717, or online at www.VictoryAssist.

Automatic Substitution Policy Around the World

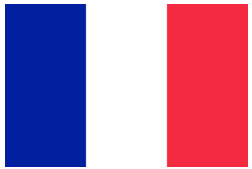
AUSTRALIA: Permits automatic substitution (“a-flagging”) of biosimilars, physicians can prevent substitution.

LATIN AMERICA: A range of policies. Where protections exist for physician prescriptive autonomy, enforcement is not consistent.

EUROPE: EMA opposes, left to member states. BANNED BY MOST STATES except for Estonia, France, Latvia, Poland and Russia. Prescriptions are generally done by INN alone.

Automatic Substitution Policy Around the World

ESTONIA: Patient can refuse and pay price difference out of pocket.



FRANCE: substitution permitted for bio-naïve patients, pharmacist-physician communication required, physician can prevent. (not yet implemented)

LATVIA: Non-bio-naïve patients can refuse and pay cost difference, physician can prevent. Others must use cheapest product.

POLAND: allowed by law, pharmacists are to discuss with patient.

Automatic Substitution Policy Around the World

GERMANY: Unless prevented by physician, pharmacists may substitute “BIOIDENTICALS” ONLY (Biosimilars to the same reference product that are made by the same manufacturer but marketed under different trade names, e.g. Inflectra and Remsima infliximab).

RUSSIA: Physicians prescribe by INN, but can prevent substitution for a medical reason. Patients can buy brand name out of pocket.

Biosimilar Substitution Policy in the U.S.

- US: 45 states permit substitution of “interchangeable” biosimilars.
- In these states, physicians can prevent substitution and are to be communicated which product was dispensed.
- FDA silent on pharmacy substitution of non-interchangeable biosimilars.
- Private payers are beginning to exclude originator products from formulary.

Recap: Interchangeability

A US-Specific higher regulatory standard to meet. More data is required.

An "INTERCHANGEABLE" Biosimilar :

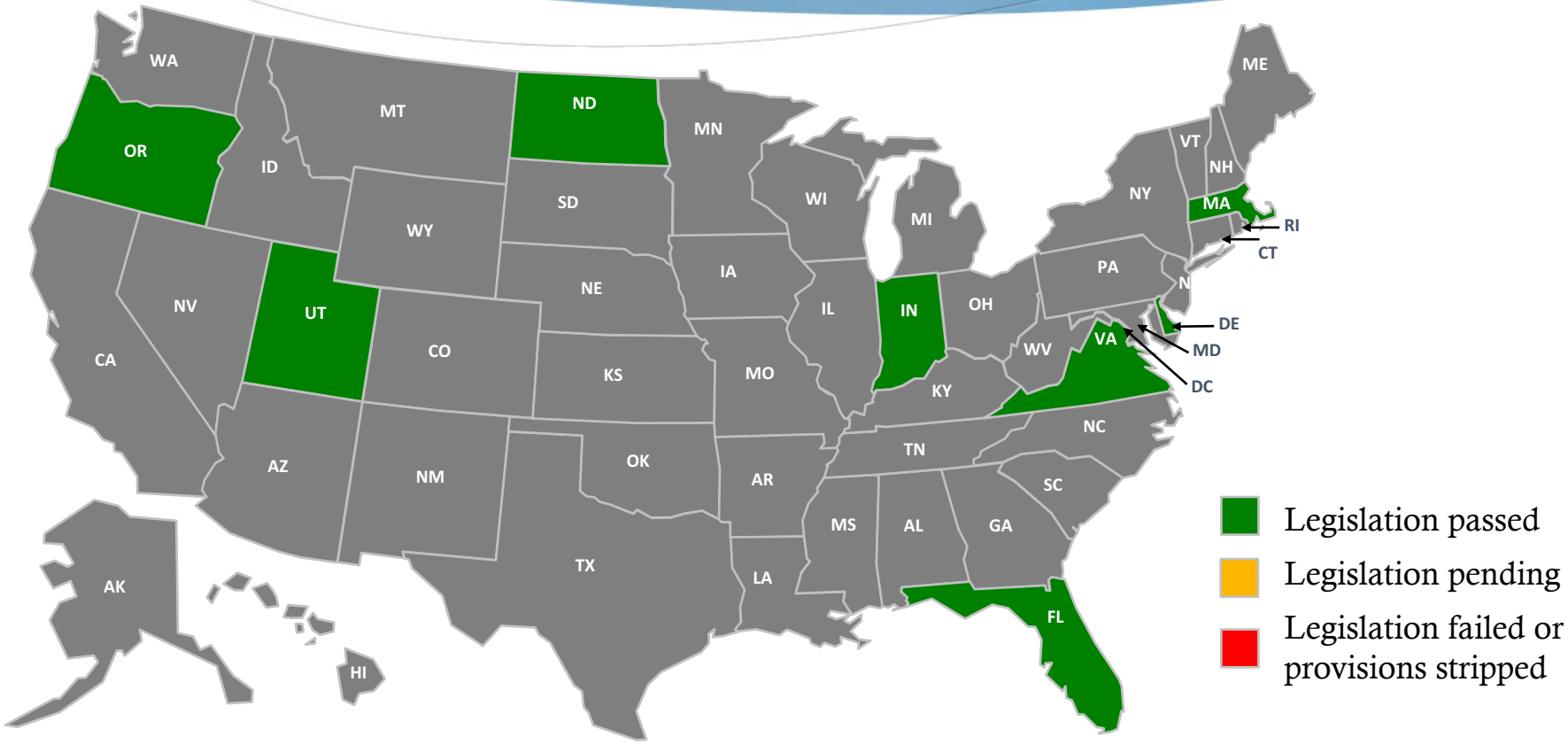
1) Must be **biosimilar** ("highly similar" to reference product).
2) Must have **same clinical result** expected as with reference product.
3) Must create **no additional risk to patient** when switching back and forth between itself and reference product.
4) **May be substituted for the reference product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

Nevertheless, 45 states and Puerto Rico have laws requiring pharmacist-physician communication when biosimilar substitution is a possibility.

Common Features of U.S. State Substitution Laws

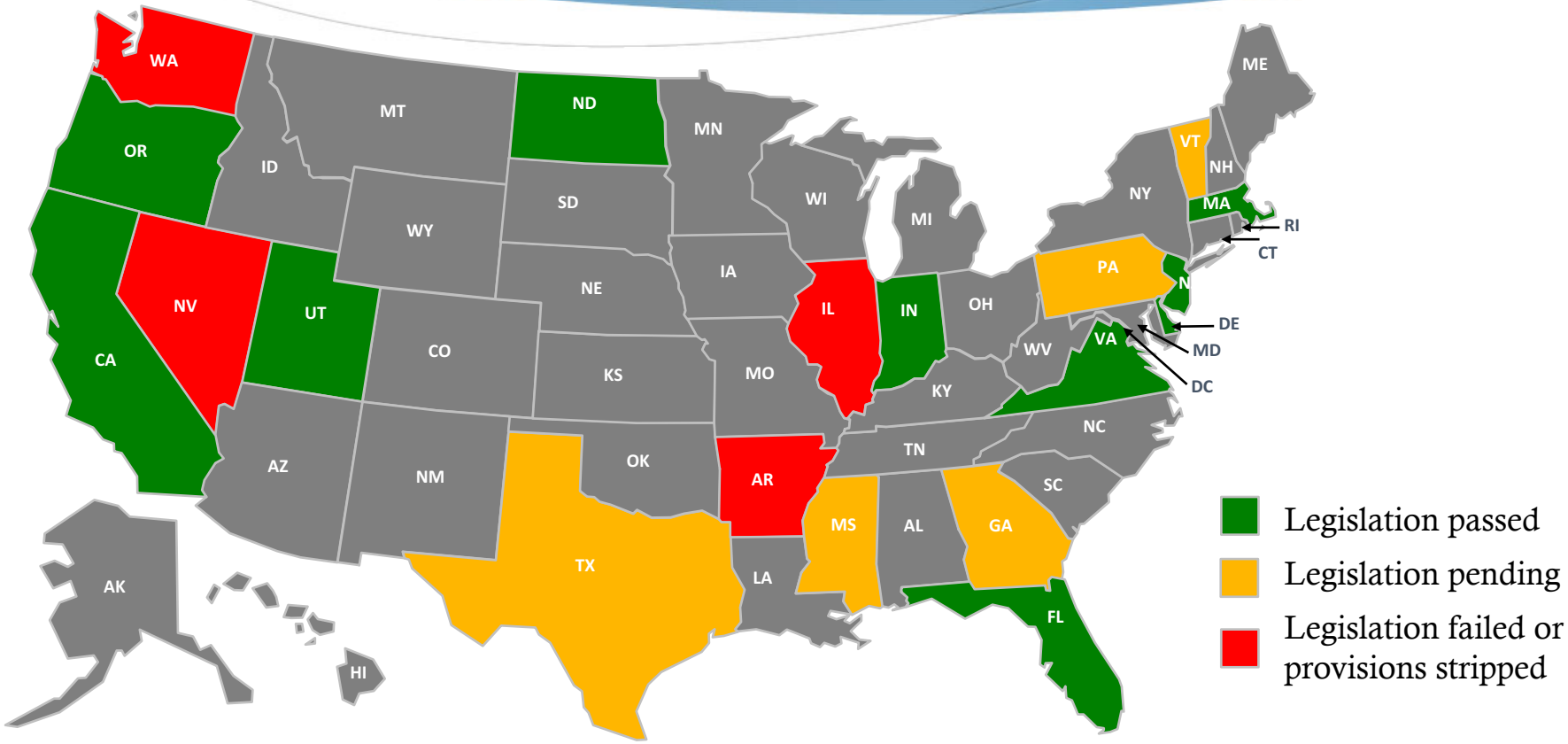
- Permits only substitution of "interchangeable" biosimilars.
- Require pharmacist to communicate which product – biosimilar or reference- was dispensed to patient within 3-5 business days.
- Allow physician to specify "do not substitute" or similar.
- Pharmacist to keep records for 2 years.

2014: Communication Requirements by State



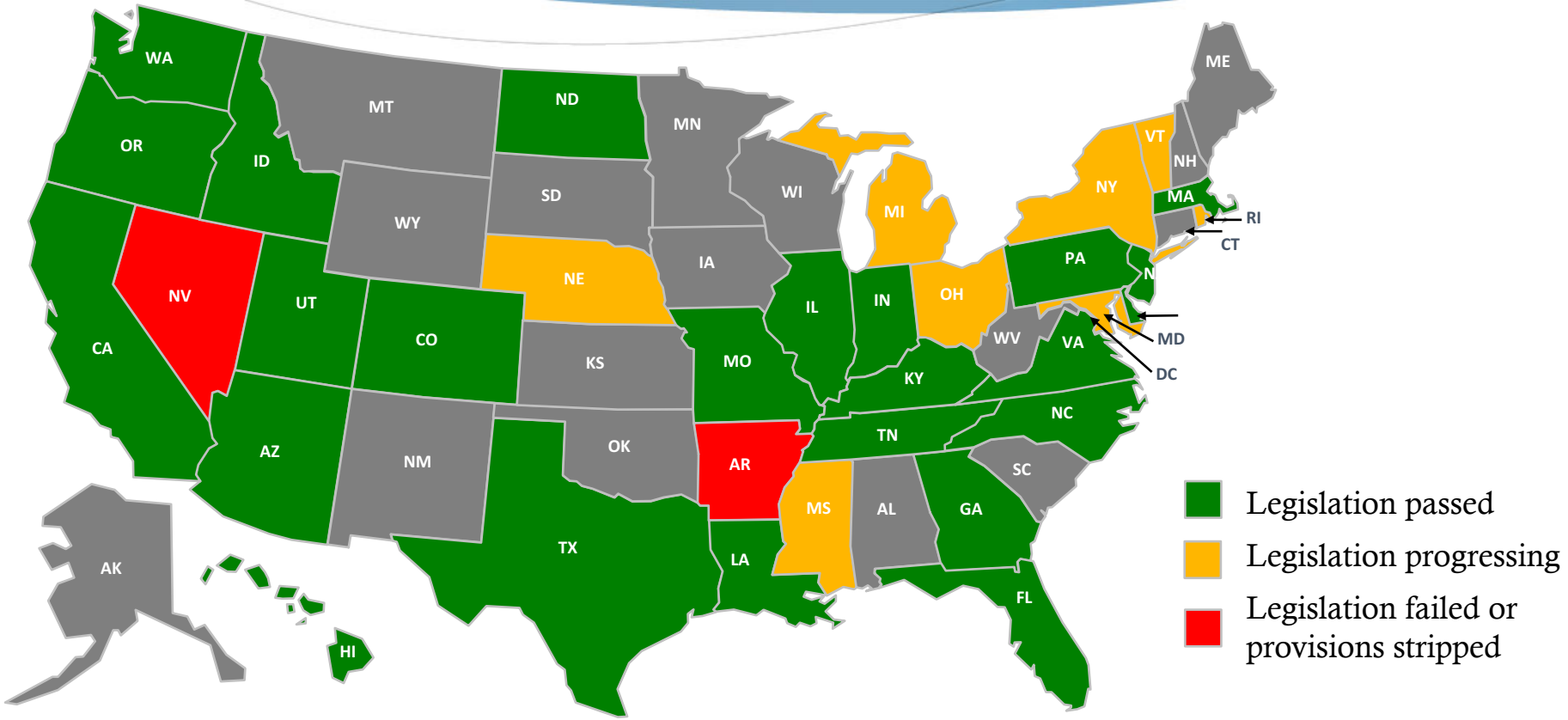
Rev. 11/15

2015: Communication Requirements by State



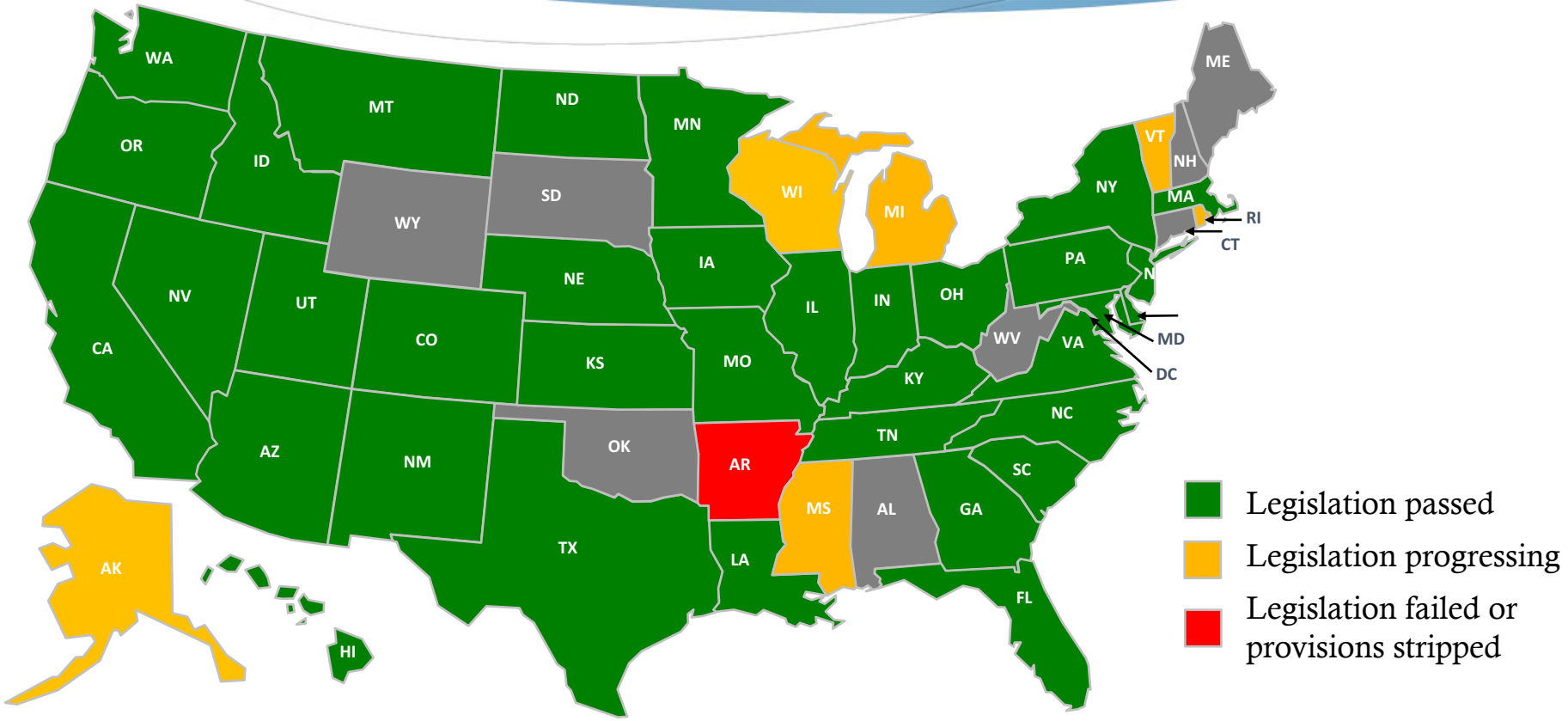
Rev. 11/15

2016: Communication Requirements by State



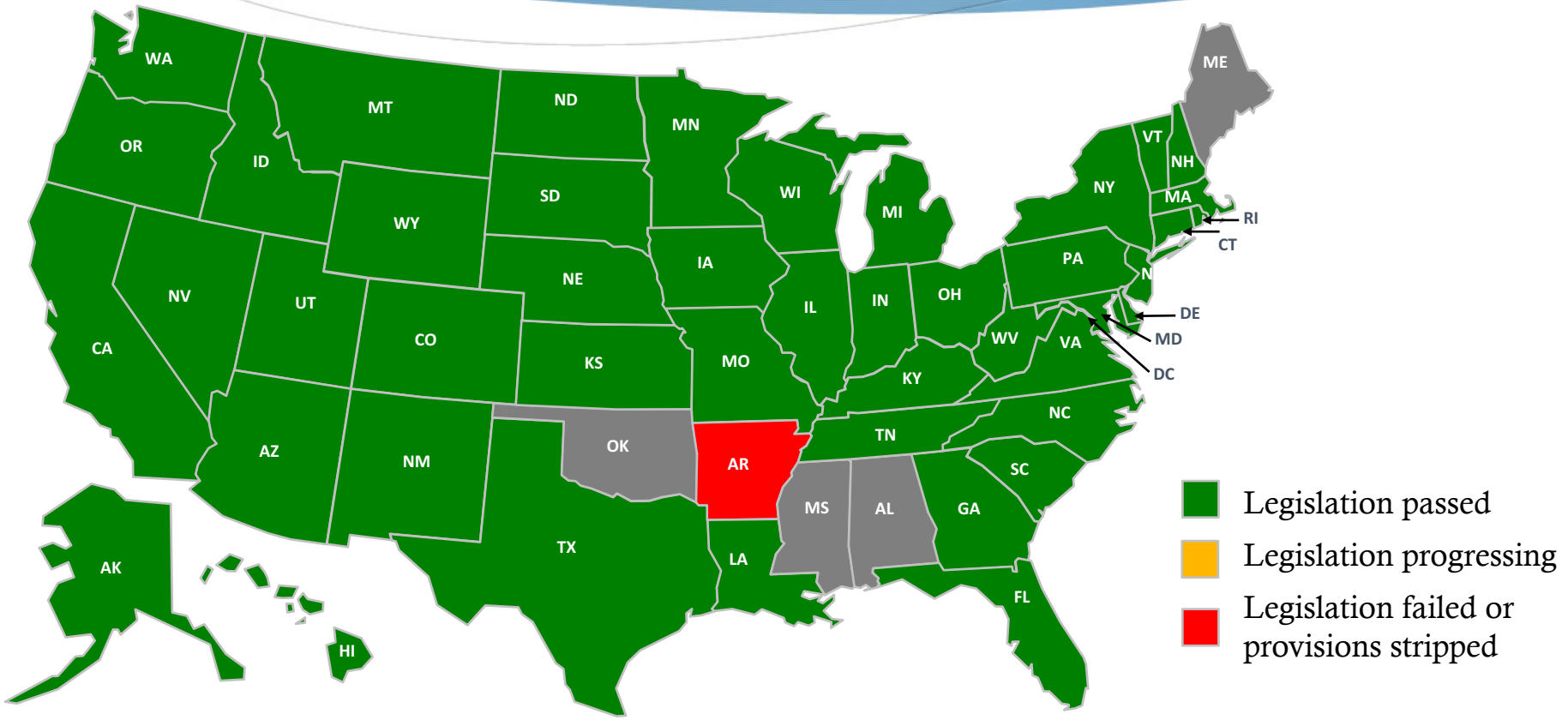
Rev. 09/14/16

2017: Communication Requirements by State



Rev. 12/17

2018: Communication Requirements by State



Rev. 09/11/18

Early Criticisms of U.S. Substitution Legislation

- Legislation premature? There are NO biosimilars in the United States marketplace.
- Premature laws create confusing patchwork of state substitution laws.
- Could legislation undermine public confidence in biosimilar medicines?

- First biosimilar approved March 6, 2015. Now 12 approved, 4 on market, and PBMs are switching patients.
- Pharmacists, physicians need to work together to educate lawmakers in remaining states, extend a common standard for these laws.
- To the contrary, Physicians defaulting to "do not substitute" as only means of knowing what patient is receiving would undermine biosimilar adoption.

Initial Resistance from Pharmacists

- Additionally, many **state pharmacy societies** had concerns that the word "notify" implied they were subservient to physicians, and preferred the word "communicate", which implies collaboration.
- **Pharmacies** also considered the initial timeframe allotted for notification, and the length of the record-keeping provisions to be onerous.
- While helping patients and physicians, bills also **empower pharmacists** to offer lower-cost alternatives to patients without seeking authorization from physicians.
- Yet as they were made aware of the benefits the communication provisions offer to patients, they have dropped their opposition and the legislation passed.

Today automatic substitution **faded as an issue of debate** among the two national pharmacy societies, ASHP and APhA.

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.

Common Ground Between Physicians and Pharmacists

- Both healthcare providers, who share concern for our patients
- Both experienced with and knowledgeable about medications
- Both incentivized to perform good pharmacovigilance
- Both want a good track-and-trace system for adverse events
- Both support good record keeping.

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

2013 Bill Language		2016-Present Bill Language
"Notification"	→	**"Communication"**
Notification **only if biosimilar substituted**	→	Communication of which biologic was was dispensed- **innovator / biosimilar**
72 hours to notify	→	**5 days** to communicate
Must retain records for **5 years**	→	Must retain records for **2 years**

Timing of Communication

- The timing of the communication process must not impose an undue burden on the pharmacist
- Communication of a substitution is after dispensing
- Must be timely enough to facilitate **accurate record keeping** and **attribution of adverse events** by the physician.

Medication-use system

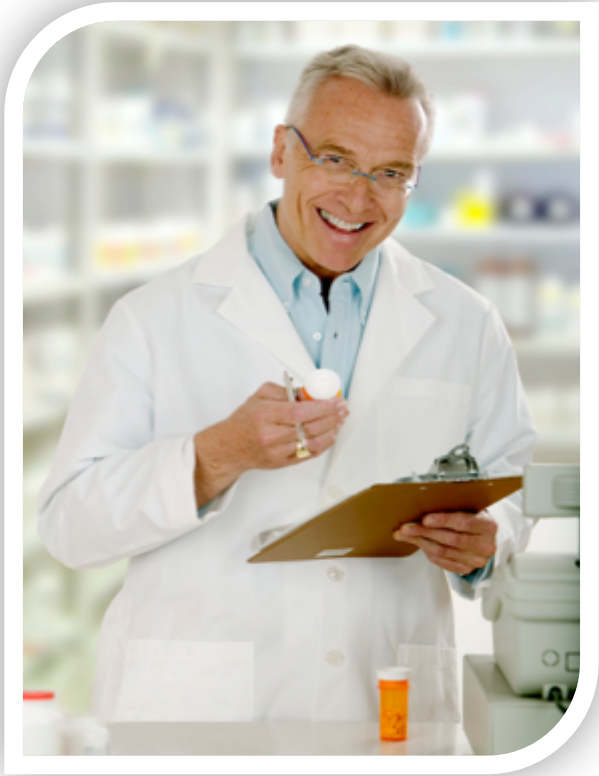
- Prescribing
- Preparation
- Dispensing
- Administration
- Monitoring

Strategies for Improving Prescribing

- Collaborative practice that includes a pharmacist
- The formulary system
- Therapeutic interchange (NOT substitution)
- Evidence-based clinical practice guidelines
- Clinical decision support systems
- Metrics and performance management
  - Effectiveness
  - Safety
  - Cost

Added Value of Pharmacists

- Prudent purchasing
- Inventory control
- Managing waste
- Managing utilization
- “Balanced scorecard” (pharmacoeconomics)
- Proactive awareness



Conclusions

- The pharmacist's responsibility does not end with the patient.
- As with vaccinations, it is a matter of responsibility to a larger community.
- Pharmacists have a larger responsibility to work collaboratively with physicians, regulators, manufacturers and others to create a strong pharmacovigilance system to protect everyone.
- Clear communication between all parties is essential for the successful rollout of biosimilars- not only in their naming, and also when they are substituted.

Thank You
For Your Attention

Learning Assessment Questions

How familiar are you with BIOLOGIC medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How familiar are you with BIOSIMILAR medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How many biosimilars been approved by the FDA for use in the U.S.?

1. None
2. ~4
3. ~12
4. ~30

“Biosimilars are structurally identical to the reference biologic product upon which they are based.”

1. TRUE
2. FALSE

“In the U.S., biosimilars share the same non-proprietary name as their reference product, as with generics.”

1. TRUE
2. FALSE
3. NOT SURE

“A biosimilar is by definition interchangeable with its reference biologic product.”

1. TRUE
2. FALSE
3. NOT SURE

“A pharmacist can substitute any FDA-approved biosimilar in place of the prescribed originator biologic”

1. TRUE
2. FALSE

“As a pharmacist, I believe I will have a role in making decisions about the choice of biologics for specific indications.”

1. YES
2. NO
3. NOT SURE

“I believe the safe use of biosimilars will reduce healthcare costs.”

1. YES
2. NO
3. NOT SURE

Which of the following tools will you use to realize the potential cost benefits of biosimilars:

1. The formulary system
2. Clinical practice guidelines that specify the choice of drugs
3. Therapeutic interchange policy
4. Patient-specific dialog with the prescriber on a case-by-case basis
5. All of the above

“I need and plan to learn more about biologics to prepare myself for a role in the safe use of biosimilars.”

1. TRUE
2. FALSE