SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES

# *Clinical Perspectives on Biosimilars*

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Presented at the Chapman University School of Pharmacy
May 29, 2015

# *Disclosures*

I have no relevant conflicting or other financial disclosures.

But, let's face it ….

I'm a pediatrician who cares for kids with rheumatic diseases and other chronic illnesses. Do you really think I have any significant financial issues to disclose?

# *One of These Things is Not Like the Others…*

# *The Promise of Biosimilars*

Biologic Medicines have improved and extended the lives of millions of patients around the world. BIOSIMILARS will offer increased access to these therapies and new treatment options for patients and their physicians.

But the COMPLEXITY of these medicines;

Their HIGH SENSITIVITY to manufacturing differences, light, heat, denaturing;

Their potential for IMMUNE REACTIONS; and,

The consequences to the patient of INADEQUATE TREATMENT, which may include IRREVERSIBLE DAMAGE,

means ***CLEAR PRODUCT IDENTIFICATION & TRACKING is ESSENTIAL.***

***Who Cares?***

***What's the Big Deal?***

***Aren't these all the same?***

***Aren't these just generics?***

If that were the case, we wouldn't be here.

Unfortunately, this is a prevailing opinion about biosimilars, if there is any thought about it at all.

But the reality is ….

There is **much** to care about.

They **aren't** the same.

They **aren't** generics.

As in life, there is much more **complexity** than we want.

The more we know, the **less we understand.**

# *Review: What Makes Biologics Special?*

# *Biologic vs. Chemical Medicines*

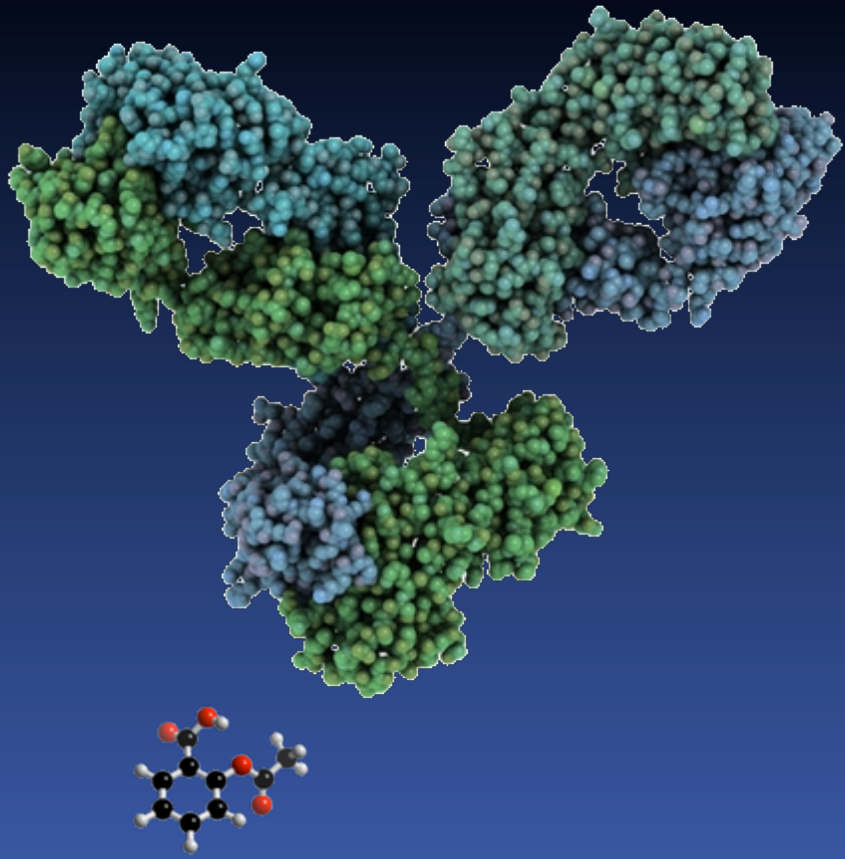
SIZE: significantly larger, potential for immunogenic reactions

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



***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"***

For Biosimilars to be successfully introduced, adopted and used, there needs to be significant and more extensive education, understanding, research and oversight to develop the physician and patient confidence in these new products.

# Areas of physician and patient concern with all biologic medications, not just Biosimilars

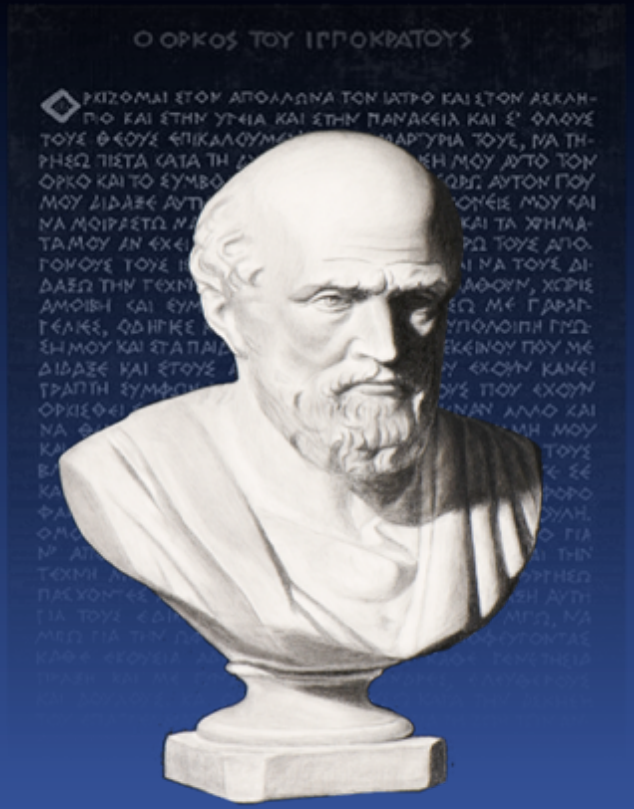
- **What medicine is the patient actually receiving?**
- **If there is a substitution:** When? By whom? To what?
- **Are the medicines really the same?** If not, how will we know? (e.g., Should biosimilars have unique nonproprietary names?)
- **What are the oversight rules:** Who is going to do it? How will it be done? Will there be regulatory consistency? How well will they protect patients?

# *A Physician's Guiding Principles*

- Patient safety is paramount.

- Information, Communication and Collaboration is critical: the more we know, the more we work together, the better we can serve our patients.

- Data, short and long term, is essential to ensure confidence in these medications and improve their appropriate use.




*Hippocratic Oath: "first, do no harm"*

***Critical Question:***

If the medications are similar but not identical, how much difference is acceptable if we are going to allow them to be used interchangeably?


*FDA will be issuing guidance in 2015 specifically on the issue of Interchangeability*

# *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.

# *Physician Concern: Interchangeability and Immune Response*

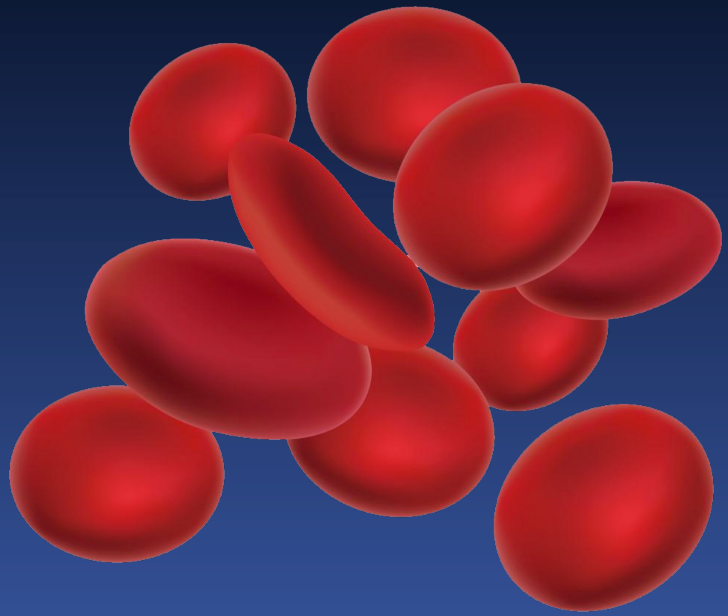
- We do not yet know if biosimilars will be as effective, more effective, or less effective than the originators.
- We do not yet know if the variations in protein structure, glycosolation, etc. will result in more or fewer adverse effects.
- We do not yet know if switching between similar molecules will induce antibodies or other potentially serious immune responses, perhaps rendering these medications ineffective—or worse.

# *Physician Concern: Interchangeability and Immune Response*

- We do not yet know how long one must allow between changing medications to adequately know if it is effective or could create problems for the patient.
- We need to have the data to know what works or doesn't for individual patients.
- We need to know which medication the patient is receiving—regardless of whether it is an originator or not—to be able to make adequate assessments regarding patient response to the medication.

# *Distinguishability is Critical for Pharmacovigilance*

- More than 30 biosimilars are now available in Thailand to stimulate red blood cell production in cancer patients.
- One (or more) caused a deadly condition known as Pure Red Cell Aplasia (PRCA).
- Since all share the same INN, being able to attribute adverse effects—and efficacy—to the correct medicine is critical.



# *Substitution Policy in the U.S.*

**CONGRESS**

- Sets legal definition
- Interchangeable: substitution without physician intervention

**FDA**

- Makes scientific decisions
- Sets Interchangeability criteria

**STATES**

- Decide what pharmacists are allowed to do

# *What is "Automatic Substitution"?*

1) Physician writes a prescription


2) Pharmacist is allowed, or required, to provide a different medicine to the patient <u>without communication with prescribing doctor beforehand</u>

# *Could "Dispense as Written" Become the Default Option?*

- Rushing biosimilars into use before rigorous quality data over time for interchangeability determination undermines physician confidence in biosimilars.
- Cutting physicians out of the treatment decision, or overruling them creates an incentive to default to "Dispense as Written."
- Thus, paradoxically, utilization of biosimilars (and any potential cost savings) **could actually be undermined** by forcing biosimilars onto patients or cutting physicians out of the loop.

# *What do Physicians Think About Substitution of Biosimilars?*

# *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.”

# *European Prescriber Survey: Physician Attitudes on Substitution*

**77%** felt NOTIFICATION OF SUBSTITUTION was “very important” or “critical.”

62% stated that it is “not acceptable” for a pharmacist to determine which biologic medicine to dispense.

**72%** felt that HAVING SOLE AUTHORITY to decide which biologic is used is “very important” or “critical.”

**74%** felt the authority to write “DISPENSE AS WRITTEN” was “very important” or “critical.”

# *Canadian Prescriber Survey: Physician Attitudes on Substitution*

**85%** felt NOTIFICATION OF SUBSTITUTION was “very important” or “critical.”

**80%** felt the authority to write “DISPENSE AS WRITTEN” was “very important” or “critical.”

**71%** felt that a PHARMACIST DETERMINATION of which biologic / biosimilar to dispense was unacceptable.

# *It's All About the Patient*

- Patients and Physicians must know what medication the patient is actually receiving in a timely fashion to appropriately assess its efficacy, determine potential adverse events (AEs), and make appropriate therapeutic decisions.
- We cannot provide quality care for our patients without knowing the specific medication the patient is actually taking.
- Communication, cooperations & collaboration between patient, pharmacist and physician is crucial.

# *What's In A Name?*

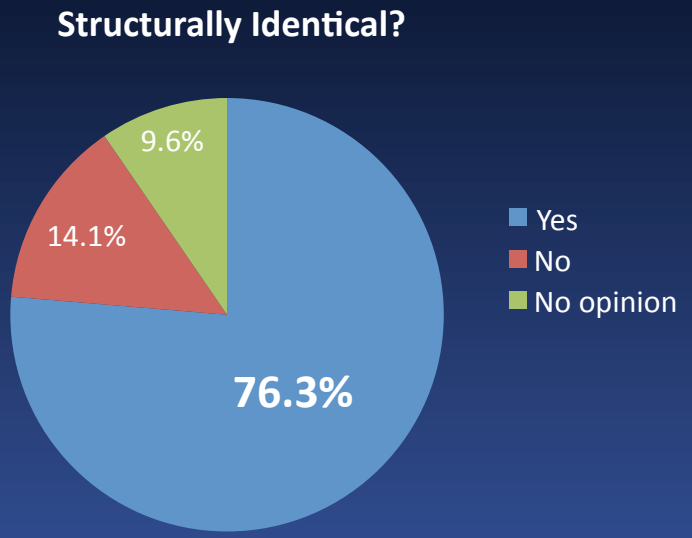
# *ASBM Surveys Identified A Need for Education… and for Clear Naming of Biologic Medicines*

Physicians' misconceptions about biosimilars, prescribing and AE reporting practices underscore a need for a clear naming system with distinguishable nonproprietary names for all biologics, including biosimilars, to facilitate intended prescribing and traceability.

EVEN where biosimilars have been available longest AND a system for tracking exists, providers still strongly support distinguishable names for ALL biologics.

# *U.S. Prescriber Survey: Physician Attitudes on Biosimilar Naming*

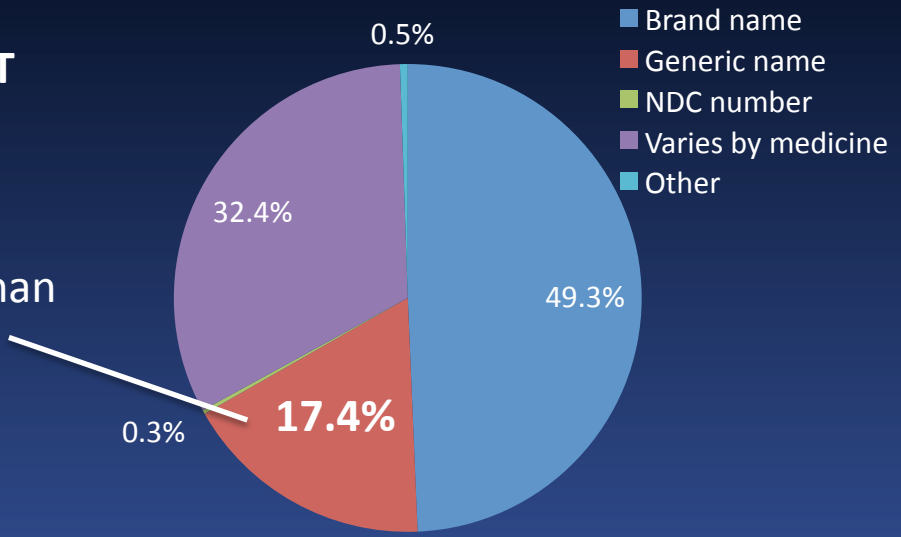
- **76%** of respondents mistakenly believe a biosimilar with an identical non-proprietary name as its reference biologic is STRUCTURALLY IDENTICAL.



# *U.S. Prescriber Survey: Physician Attitudes on Biosimilar Naming*

**WHEN IDENTIFYING MEDICINES IN PATIENT RECORD:**

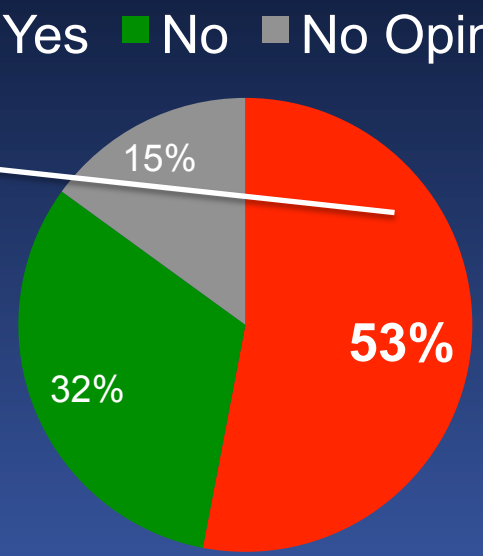
- **<u>17% use INN only</u>**, which could result in patients receiving a different medicine than the physician intended or thought was prescribed.



# *E.U. Prescriber Survey: Physician Attitudes on Biosimilar Naming*

- **53%** of respondents <u>mistakenly believe</u> a biosimilar with an identical non-proprietary name as its reference biologic is STRUCTURALLY IDENTICAL.
- **61%** of respondents believe a biosimilar with an identical non-proprietary name as its reference biologic is APPROVED FOR THE SAME INDICATIONS (*This may or may not be true.)*

*"If two medicines have the same non-proprietary scientific name, does this suggest to you or imply that the medicines are structurally identical?" (N=470)*




# *E.U. Prescriber Survey: Physician Attitudes on Biosimilar Naming*

**WHEN IDENTIFYING IN PATIENT RECORD:**

- **Only 32% of respondents** use brand name and non-proprietary name (INN) to identify the exact biologic being prescribed
- **24% use INN only**, which could result in patients receiving a different medicine than the physician intended or thought was prescribed.

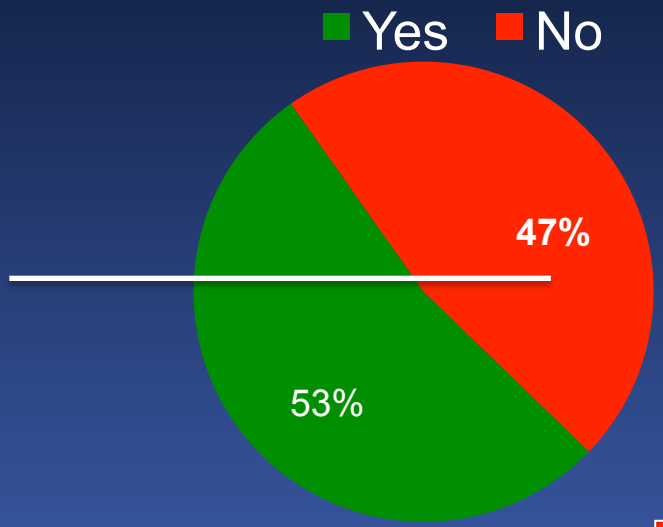
**WHEN REPORTING ADVERSE EVENTS:**

- **27%** of prescribers NEVER include the batch number
- **33%** only SOMETIMES include the batch number
- **40%** ALWAYS include the batch number

# *Canadian Prescriber Survey: Physician Attitudes on Biosimilar Naming*

- **64%** of respondents mistakenly believe a biosimilar with an identical non-proprietary name as its reference biologic is STRUCTURALLY IDENTICAL.
- **47%** of respondents believe biosimilar with an identical non-proprietary name as its reference biologic is APPROVED FOR THE SAME INDICATIONS (*This may or may not be true.)*

*"Are you aware that a subsequent entry biologic may be approved for several or all indications of the reference product on the basis of clinical trials in only one of those indications?" (N=427)*



# *Canadian Prescriber Survey: Physician Attitudes on Biosimilar Naming*

**WHEN IDENTIFYING IN PATIENT RECORD:**

- **17% of respondents** use non-proprietary name (INN) to identify the exact biologic being prescribed, which could result in patients receiving a different medicine than the physician intended or thought was prescribed.

**WHEN REPORTING ADVERSE EVENTS:**

- **26% use INN only**, which could result in misattribution or pooling of adverse events
- **45%** of prescribers NEVER include the batch number
- **29%** only SOMETIMES include the batch number
- **26%** ALWAYS include the batch number

# *So…What's the Point?*

Given the complexity of these medications, their potential adverse effects, and the long-term potential outcomes of inadequate treatment, it is ESSENTIAL that EVERYONE involved in the care of patients receiving biologics adequately and appropriately communicate, cooperate, and collaborate in the manufacturing, distribution, and use of these agents.

## *Again, It's All About the Patient*

Therefore, we believe it essential that:

- Patients
- Pharmacists
- Payers
- Physicians
- Manufacturers
- Regulators

<u>Must be on the same page</u> regarding the identification and use of these medications

# *Distinguishable Naming*

# *The Role of Names in Pharmacovigilance and Safety*

**IDENTIFICATION**

- Patients, physicians, and pharmacists should be able to **accurately identify the product (by manufacturer or brand name), ensure it is the intended prescription, and avoid inadvertent substitution.**

- A biosimilar should be **distinguishable both from its reference product and from other approved biosimilars that reference the same biologic.**

# *The Role of Names in Pharmacovigilance and Safety*

**PHARMACOVIGILANCE**

- Distinguishable naming helps differentiate **products for observing and reporting adverse events.**
- **Tracking and tracing of biologics** is more challenging than with chemical drugs. An adverse impact from a biologic may take months to be recognized.
- **Multiple means of product identification** avoid a single point of information failure.

**MANUFACTURER RESPONSIBILITY**

- Patient response, good or not-so-good, should be traceable to the correct manufacturer's product.
- This helps everyone better understand the effects of each medicine and make improvements as needed.

# *The WHO Solution: The "Biological Qualifier" (BQ)*

A random string of letters added to the International Nonproprietary Name (INN) of the biologic, allowing it to be distinguishable from similar biologics. Similar systems are in place in Australia and Japan.

Since 2012, ASBM has been working closely with the WHO as it develops its standard for distinguishable naming, sharing physician perspectives from our surveys and offering our recommendations.

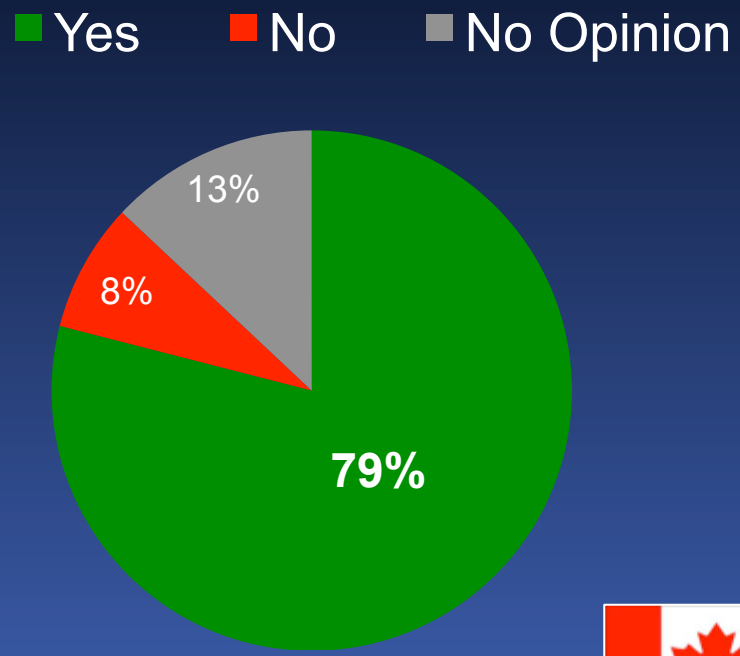
Dr. Gewanter and Dr. Schneider presented in April 2015 and will be participating in the June 2015 meeting as well.

World Health Organization

# *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)*



# *ASBM and 70+ Patient Groups Write FDA in Support of Distinguishable Naming*

In August 2014, The Alliance for Safe Biologic Medicines (ASBM), along with dozens of patient organizations, wrote Commissioner Hamburg to encourage the FDA to follow the WHO's lead, to adopt a policy of **distinguishable nonproprietary names for biosimilars** and to issue guidance reflecting distinguishable naming as a priority for the well-being of patients.

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ALLIANCE for SAFE BIOLOGIC MEDICINES

August 14, 2014

The Honorable Margaret Hamburg
Commissioner
Food and Drug Administration (FDA)
10903 New Hampshire Avenue
Silver Spring, MD 20993

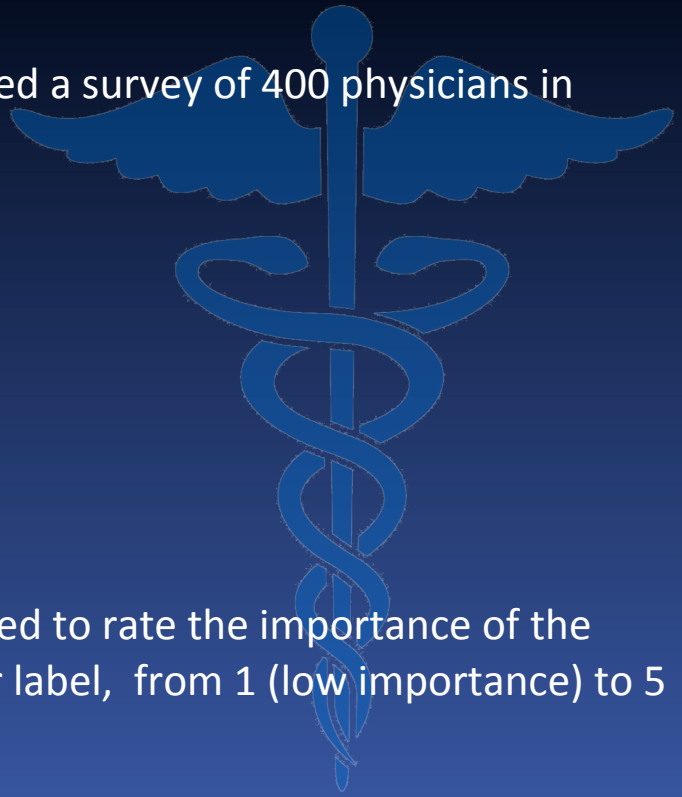
Dear Commissioner Hamburg:

On behalf of the Alliance for Safe Biologic Medicines (ASBM) and the dozens of patient organizations listed below, **we are writing to encourage the FDA to adopt a policy of distinguishable nonproprietary names for biosimilars, and to issue guidance reflecting distinguishable naming as a priority for the well-being of patients.**

In light of the recent announcement that the FDA has accepted the first application for a

# *Biosimilar Labeling*

# *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 of 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 a 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: 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, I wrote a letter to Acting FDA Commissioner Stephen Ostroff, MD—sharing our labeling survey results and our concerns with the lack of transparency in Zarxio's labeling.
- I also commended the FDA for the distinguishable naming of Zarxio, and encouraged them to continue this practice.

*Acting FDA Commissioner Stephen Ostroff, MD*

- **"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."**

# *Summary: Key Findings of ASBM Physician Surveys*

- There is a need for further education about biosimilars among physicians in the U.S., Europe, Canada, and therefore, worldwide.
- It is important to physicians that they retain the authority to use “do not substitute” to ensure the patient receives their chosen medicine.
- It is important to physicians they be informed in a timely fashion the actual medicine received by the patient.
- Distinguishability in naming is important to the practicing physicians in the U.S., Europe and Canada.
- U.S. Physicians wish for more transparency in biosimilar labeling than is currently required.

# *One of These Things is Not Like the Others…*

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*Thank You For Your Attention*