SafeBiologics
ALLIANCE for SAFE BIOLOGIC MEDICINES

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

The Biosimilar Red Tape Elimination Act:

Weakening FDA Regulatory Standards for Biosimilars, Undermining Physician Confidence, and Jeopardizing Patient Health

October 31, 2024

Webinar Overview

- **This is third ASBM Webinar on Interchangeable Biosimilars. The first two were informational.**
- This webinar seeks to provide a fair and objective assessment of Senate Bill 2305 “The Biosimilar Red Tape Elimination Act”
- To do so we will examine physician, pharmacist, regulator, and patient perspectives on the legislation.

Physician Perspectives

Ralph McKibbin, MD FACP FACG AGAF

Establishing Biosimilarity: An Abbreviated Pathway

- A biosimilar is a biologic that is **highly similar to and has no clinically meaningful differences from an existing FDA-approved biological medication** (the "reference product")
- The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar and its reference product, **not to independently establish the safety and effectiveness of the proposed biosimilar**. This generally means that biosimilar manufacturers **do not need to conduct as many expensive and lengthy clinical trials**.
- The abbreviated pathway involves an **extensive structural and functional comparison of the biosimilar and the reference product**.

Source: https://www.fda.gov/media/151061/download?attachment

Data Requirements: Biosimilarity

- **FDA evaluates each biosimilar on a case-by-case basis** and advises manufacturers on the scope and extent of testing needed to show biosimilarity. **There is no one-size-fits-all approach to biosimilar product development.**

- **Analytical studies establish structural and functional similarity.**

Other studies may include:

- **Animal studies** for toxicology or pharmacology information.
- **Clinical pharmacology studies** to demonstrate that the proposed biosimilar moves through the body in the same way and provides the same effects as the reference product.
- **Additional clinical studies** to address any remaining uncertainty about whether the proposed biosimilar has no clinically meaningful differences from the reference product.

Source: https://www.fda.gov/media/151061/download?attachment

Additional Data Requirements: Interchangeable Biosimilars

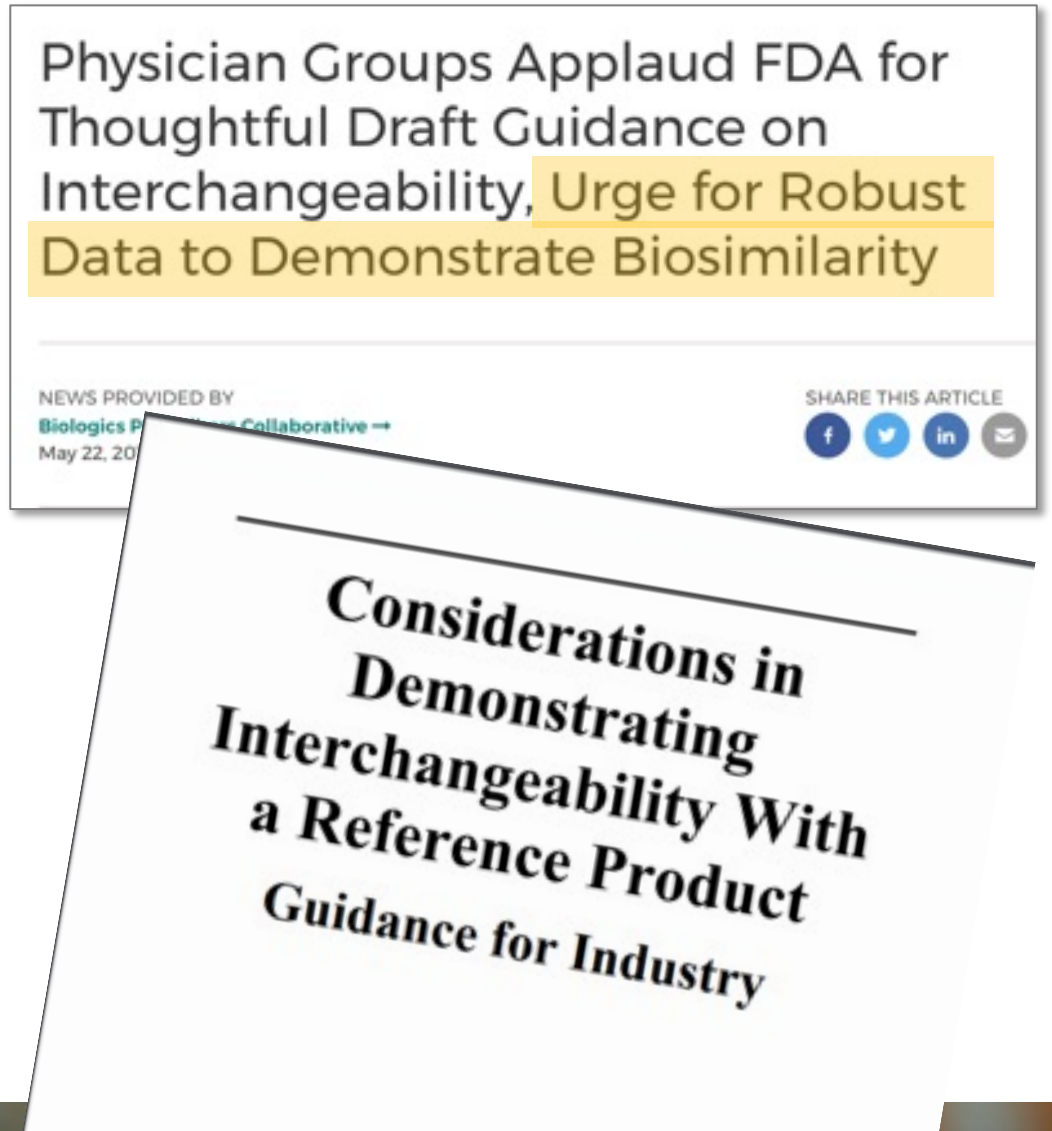
- Biosimilar products that meet additional requirements may be approved as **interchangeable** products, **which means they may be substituted for the reference product at the pharmacy level, depending on state pharmacy laws. (In all 50 states, only interchangeable biosimilars may be substituted without prior physician authorization-** we will discuss more about this later).
- In addition to establishing biosimilarity, **the manufacturer demonstrates that switching between the two products would not increase safety risks or decrease effectiveness.**
- This **may** be done by a **switching study** in which a patient alternates between the reference product and the interchangeable product multiple times over a specific period of time.
- **The FDA has the flexibility to determine whether a switching study is warranted,** depending on the data provided by the manufacturer.
- **There are currently 15 approved interchangeable biosimilars- for some, the FDA has required switching studies, for some it has not.**

Source: https://www.fda.gov/media/151061/download?attachment

Many U.S. Physician Groups Offered Comments Supportive of the FDA's Interchangeability Guidance

These included:

- American Association of Clinical Endocrinologists
- American College of Rheumatology
- American Gastroenterological Association
- Biologics Prescribers Collaborative
- Coalition of State Rheumatology Organizations



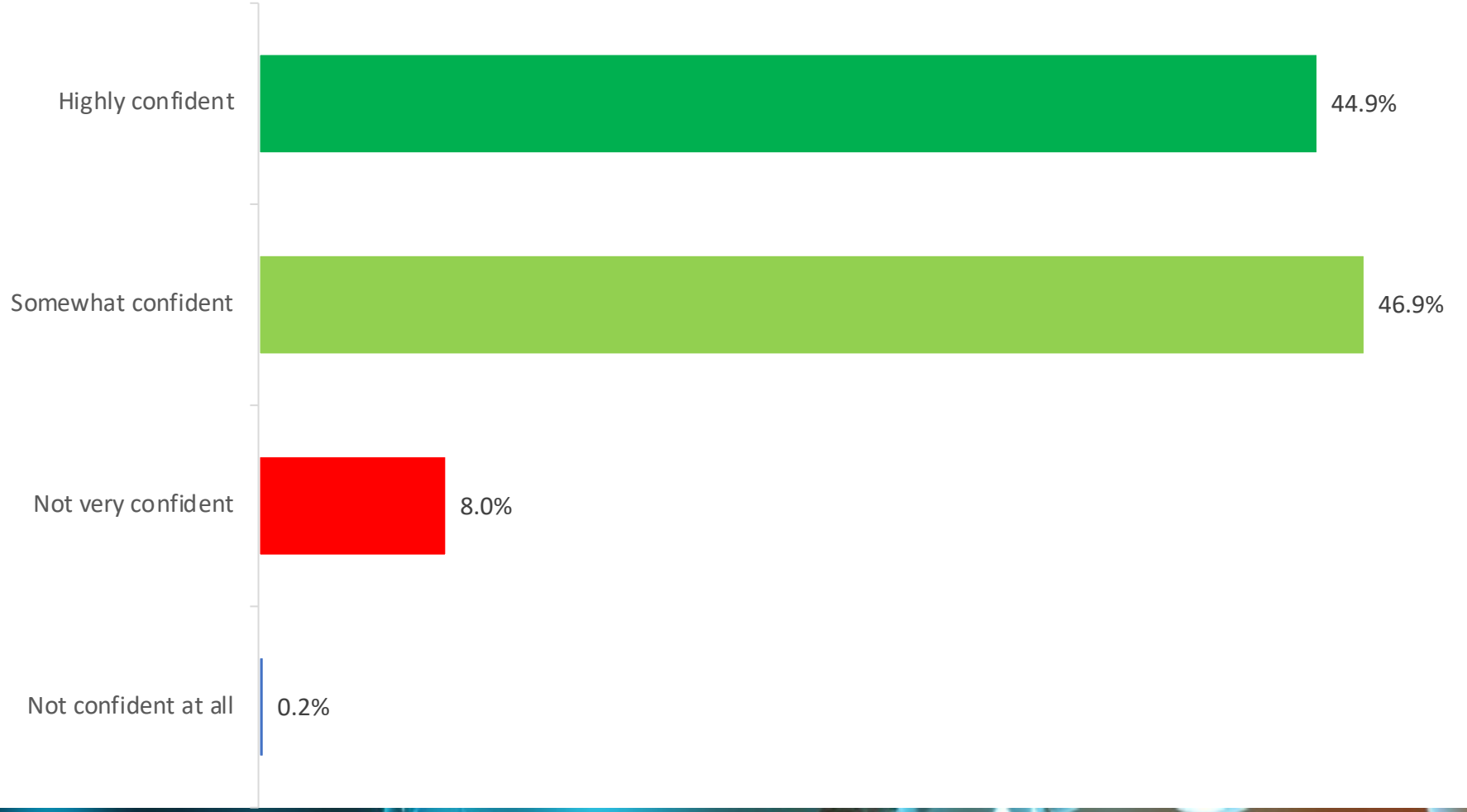
"Interchangeable": Different Meaning in U.S. and Europe

- **The European use means "substitutable by the prescriber"**
- **In the U.S., as in Europe, ALL BIOSIMILARS are substitutable by the prescriber.**
- **The U.S. "interchangeable biosimilar" category refers to biosimilars that are also substitutable by a pharmacist, due to having provided additional data to FDA showing that switching to the biosimilar will not impact the safety or efficacy for the patient.**
- **Automatic pharmacy substitution of biosimilars in Europe is rare, and often banned.**

https://safebiologics.org/wp-content/uploads/2023/11/ IC-EUvsUS-FNL.pdf

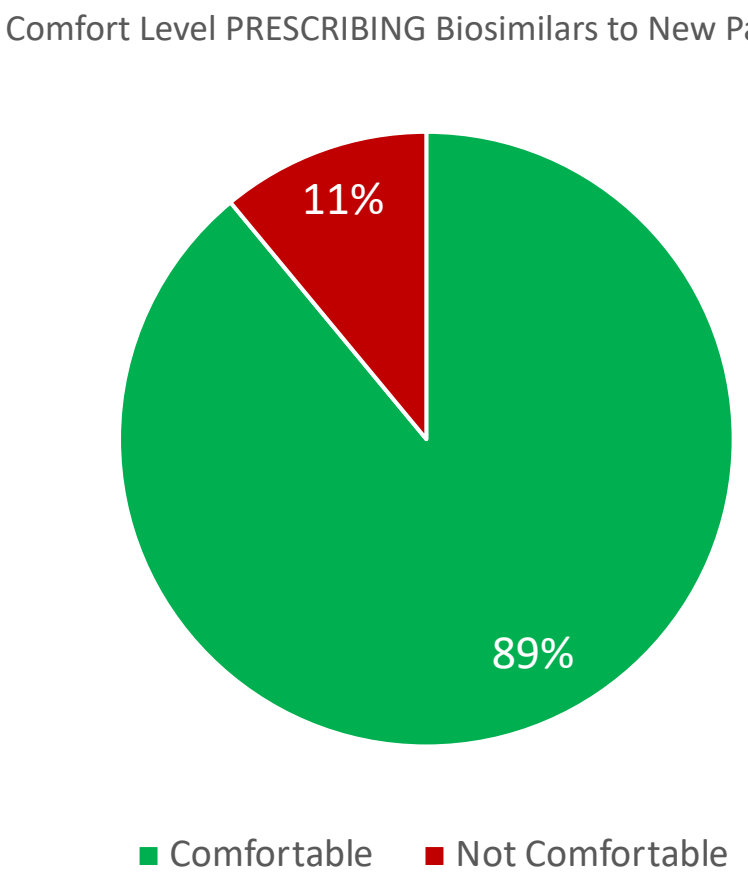
2021 Survey (n=401) U.S. Physicians Are Very Confident in Biosimilars

- Q1. How would you describe your personal confidence level in the safety and efficacy of biosimilars? (n=401)



92% expressed confidence in the safety and efficacy of biosimilars.

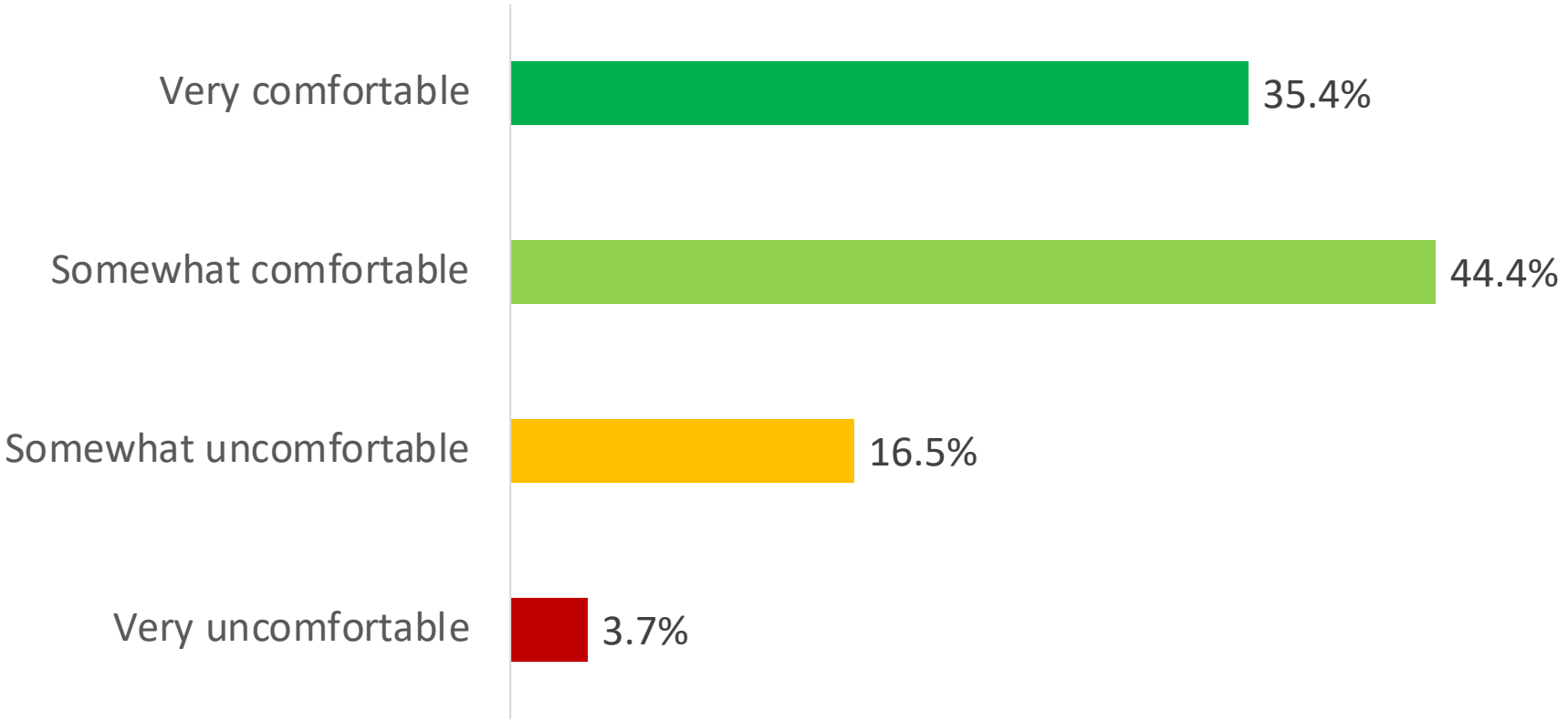
U.S. Physicians Are Very Comfortable Prescribing Biosimilars to New Patients (n=401)



Physician confidence in and comfort with biosimilars is high- the vast majorities of physicians have no concerns with prescribing biosimilars- to new patients.

US Physicians Are Generally Comfortable Switching A Patient to a Biosimilar…
…if they are leading the switch:

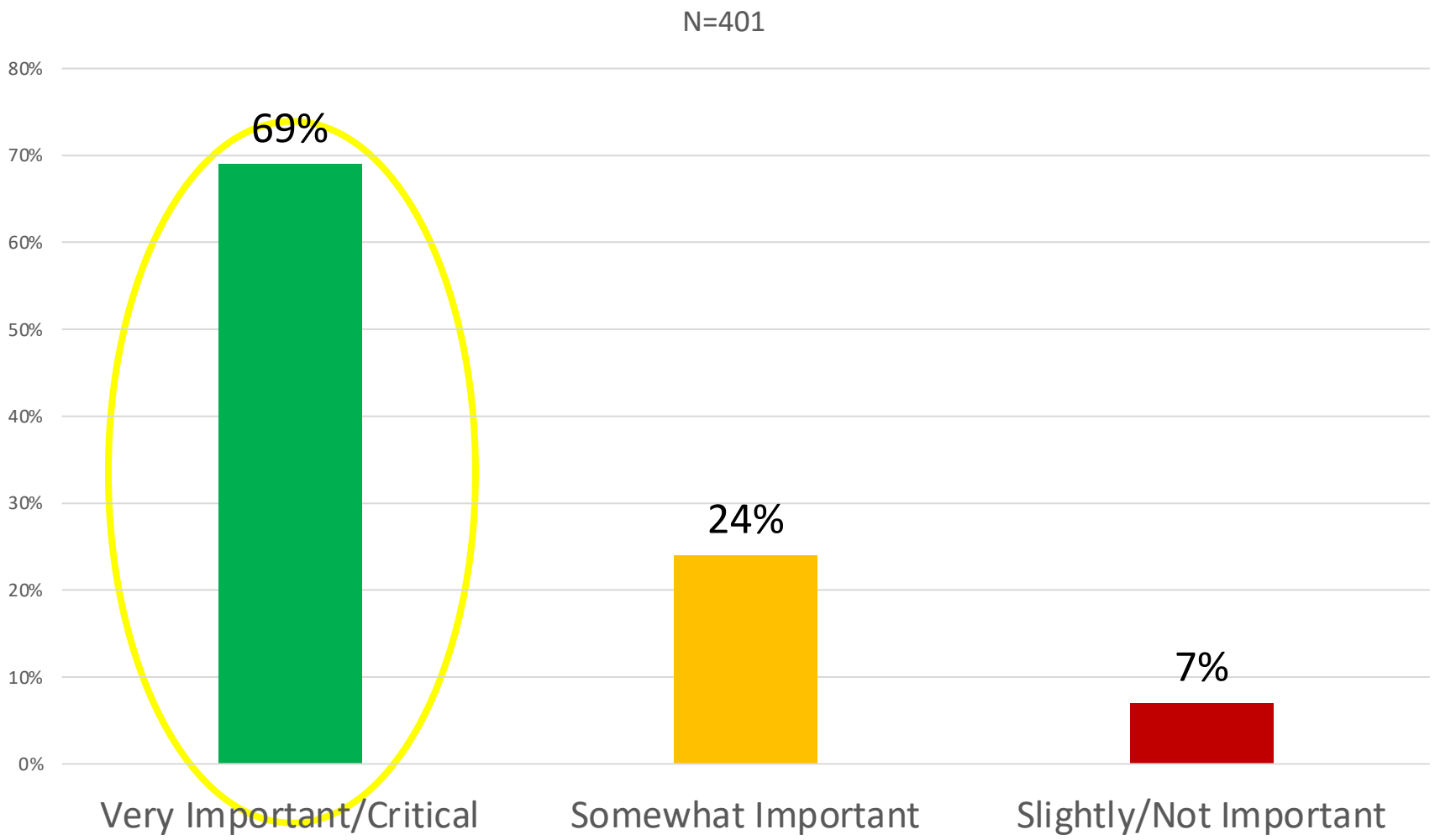
- Q4. How comfortable are you with **switching a stable patient from an originator medicine to a biosimilar?** (n=401)



80% of respondents are comfortable, to some degree, with switching a patient to a biosimilar.

However, 20% are not comfortable doing so.

Importance of Physician/Patient Control of Treatment Decisions

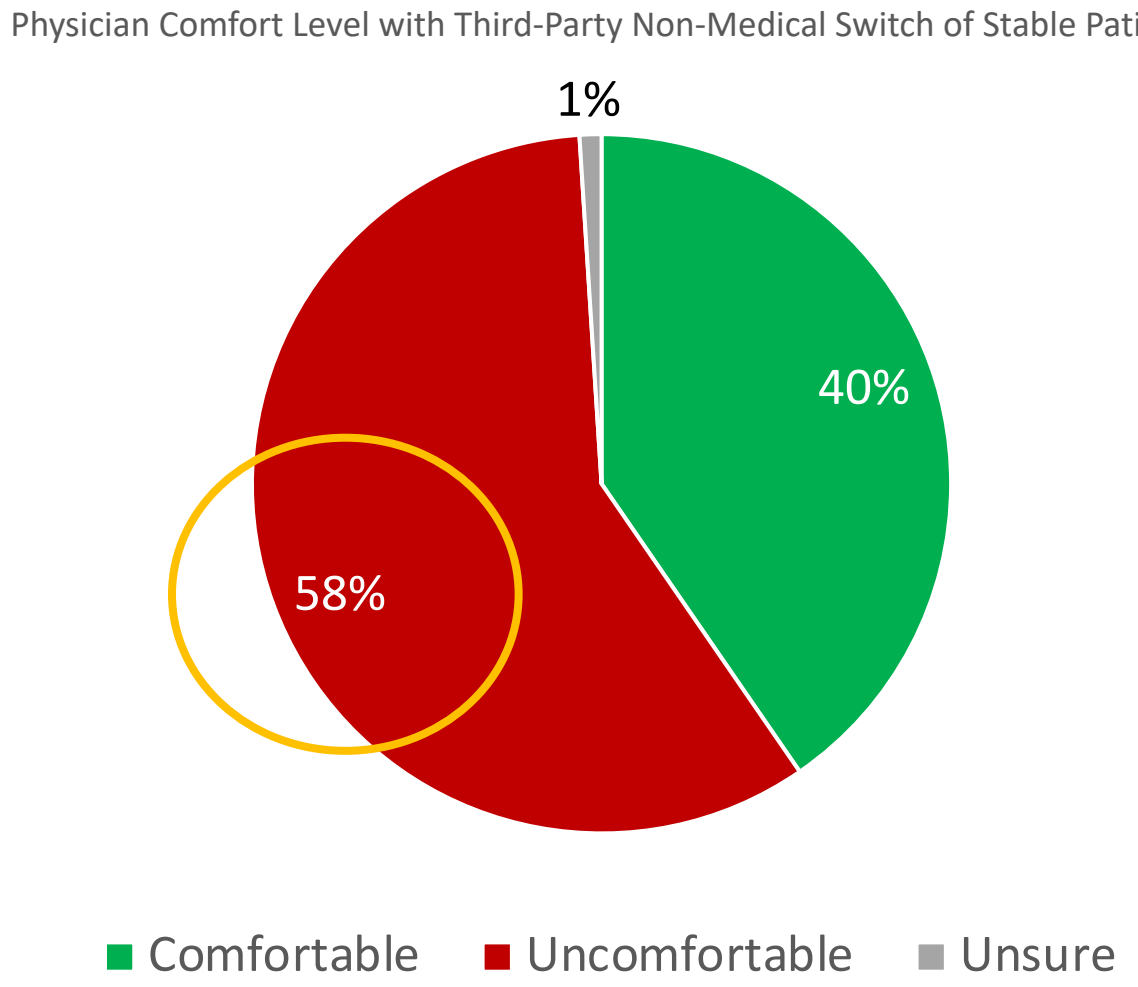


A strong majority of U.S. physicians agree it is **very important- or CRITICAL** – that the **physician, with the patient, decides which treatment option to use -** rather than a third party.

The Issue: Treatment Plans Are Not Universal. One-Size Does NOT Fit All.

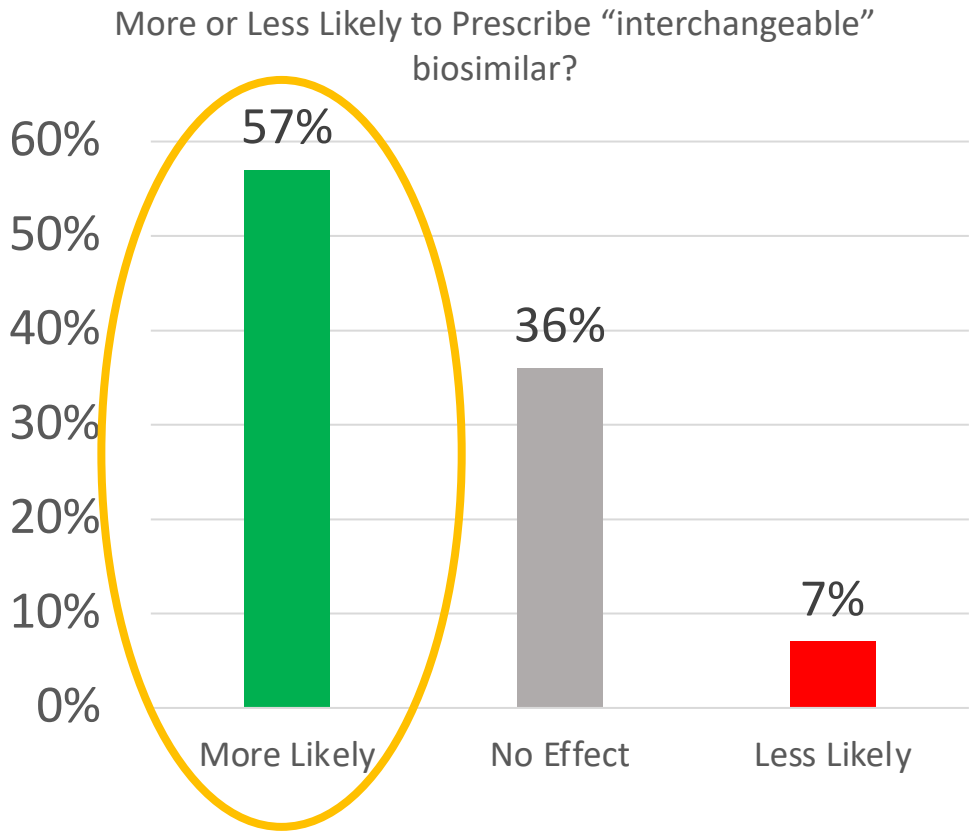
- In many cases, a patient goes through **several rounds of trial and error with their physician to find the right treatment** that works best for them.
- **This process often takes several years.**
- **This is the basis of the doctor-patient relationship.**

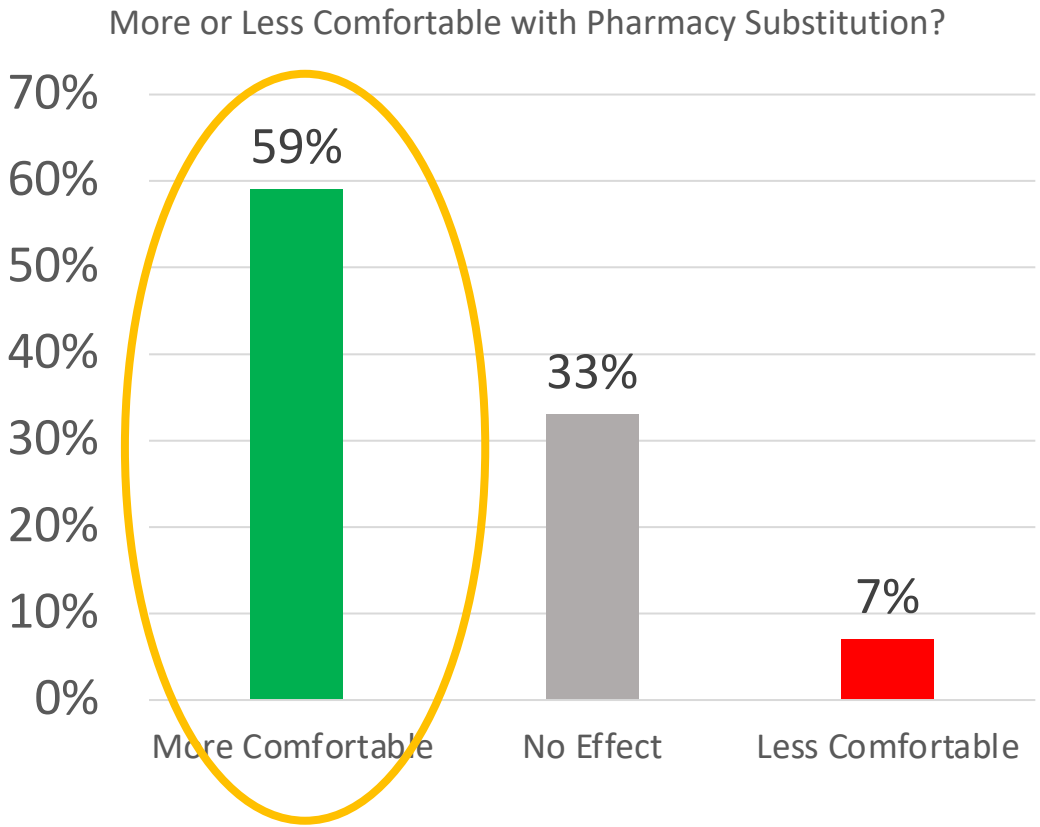
Majority of U.S. Physicians Are Not Comfortable with Third Party Non-Medical Switching of a Stable Patient



The majority of U.S. physicians, 58% are NOT comfortable with Third Party Non-Medical Switching for a patient who is stable on their current treatment.

But the DATA Currently Supporting the U.S. "Interchangeable" Designation Increases *Physician Comfort With Prescribing, Substitution*





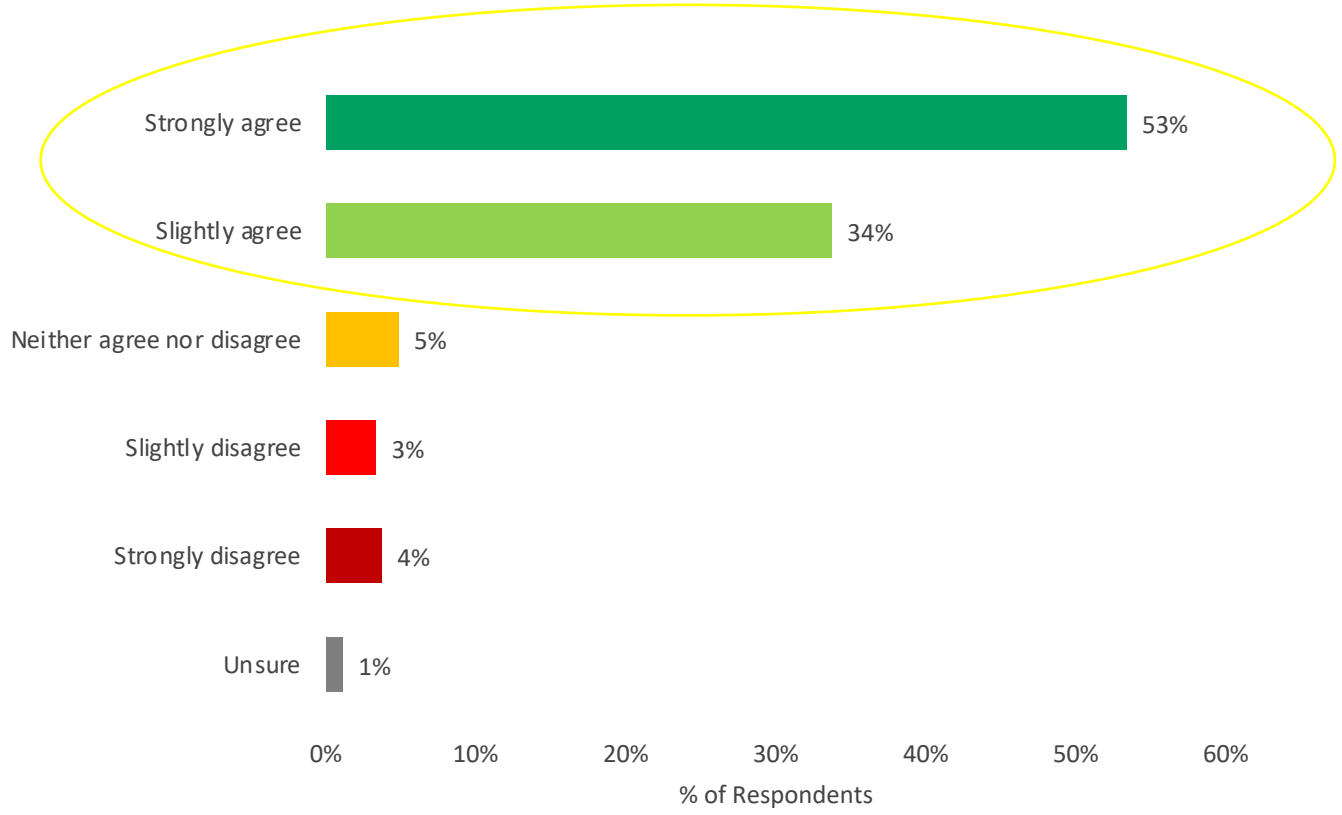
57% were more likely to prescribe a biosimilar that is interchangeable; 59% were more comfortable with an interchangeable being substituted in place of the prescribed originator product.

2024 Survey (N=270) Finds Physicians Strongly Oppose Provisions of Biosimilar Red Tape Elimination Act

- 270 participants
- All participants practice medicine in the United States
- 9 practice areas were included: Dermatology, Endocrinology, Gastrointestinal, Immunology, Nephrology, Neurology, Oncology, Ophthalmology, and Rheumatology
- Respondents distributed roughly equally between practice areas.

Comfort with Switching if Biosimilar Has Been Specifically Evaluated

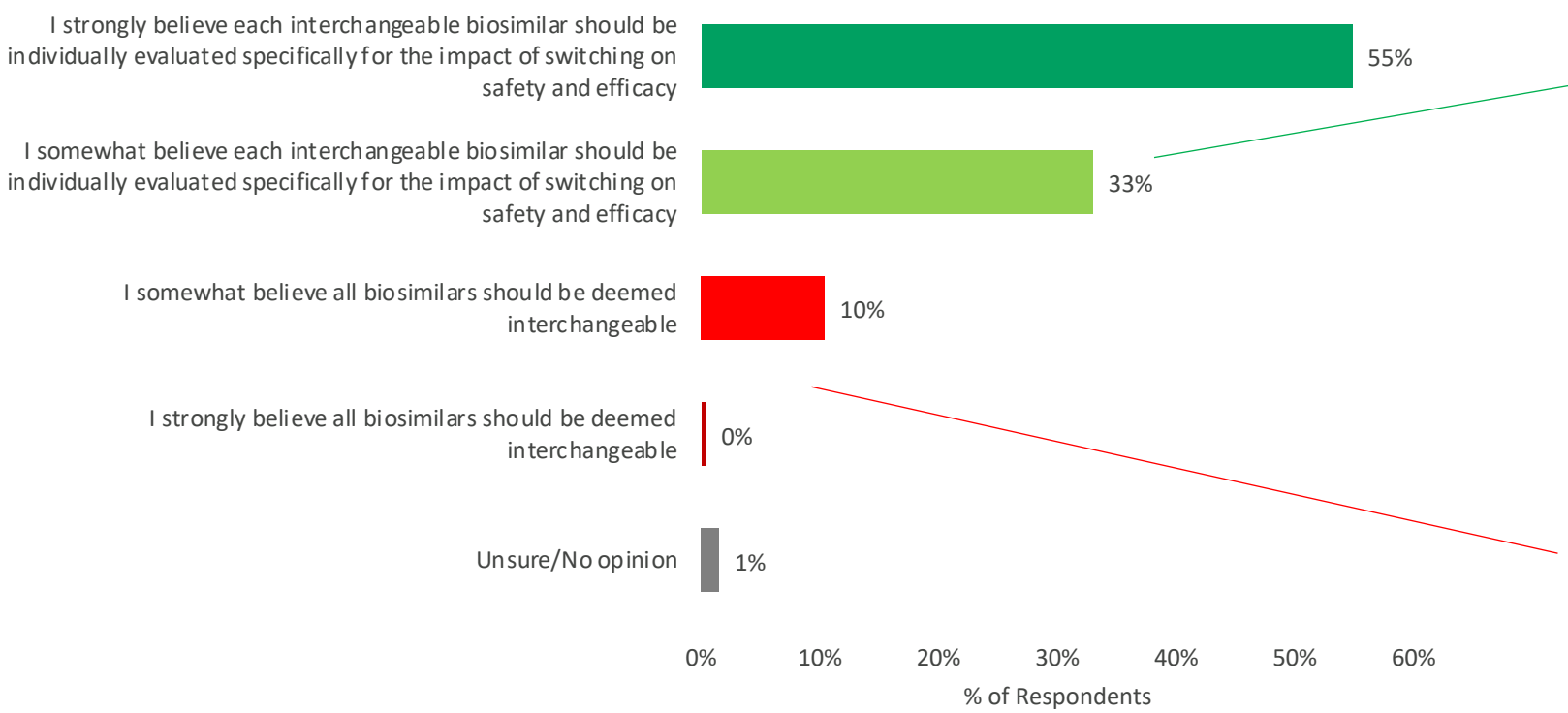
Q1. To what extent do you agree with the following statement: "I am more comfortable switching a patient from an originator biologic to a biosimilar if that medicine has been specifically evaluated for the impact of switching on safety and efficacy." (n=270)



- 87% of respondents agreed that they are more comfortable switching a patient from an originator biologic to a biosimilar if that medicine has been specifically evaluated for the impact of switching on safety and efficacy.

Whether Interchangeable Biosimilars Should Be Individually Evaluated

Q2. "Which of the following statements best represents your opinion on deeming biosimilars as interchangeable with the original biologic product:" (n=270)

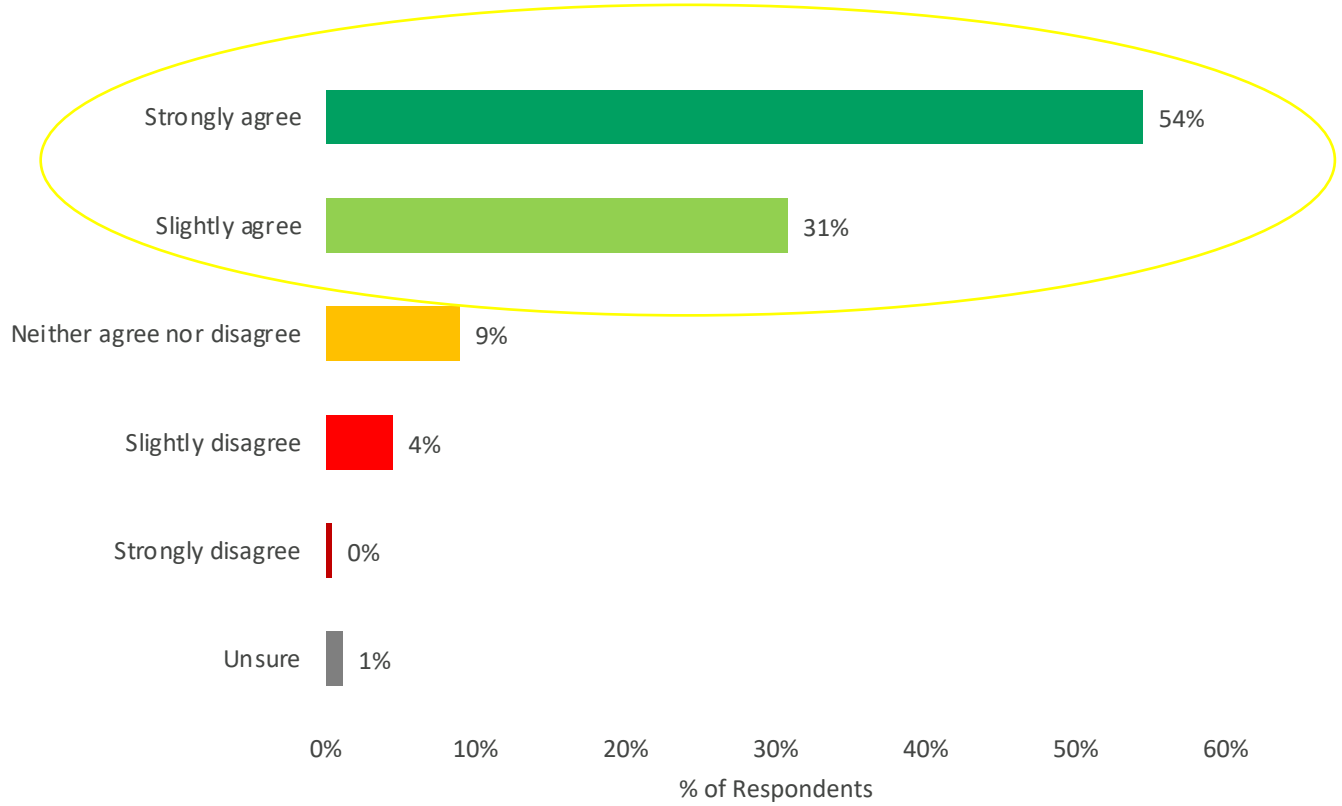


- 88% of respondents believe each interchangeable biosimilar should be individually evaluated specifically for the impact of switching on safety and efficacy.
- Only 11% believe all biosimilars should be deemed interchangeable.

Note: The words each and all were underlined in the response options when respondents took the survey.

Whether Only Individually Evaluated Biosimilars Should Be Deemed Interchangeable

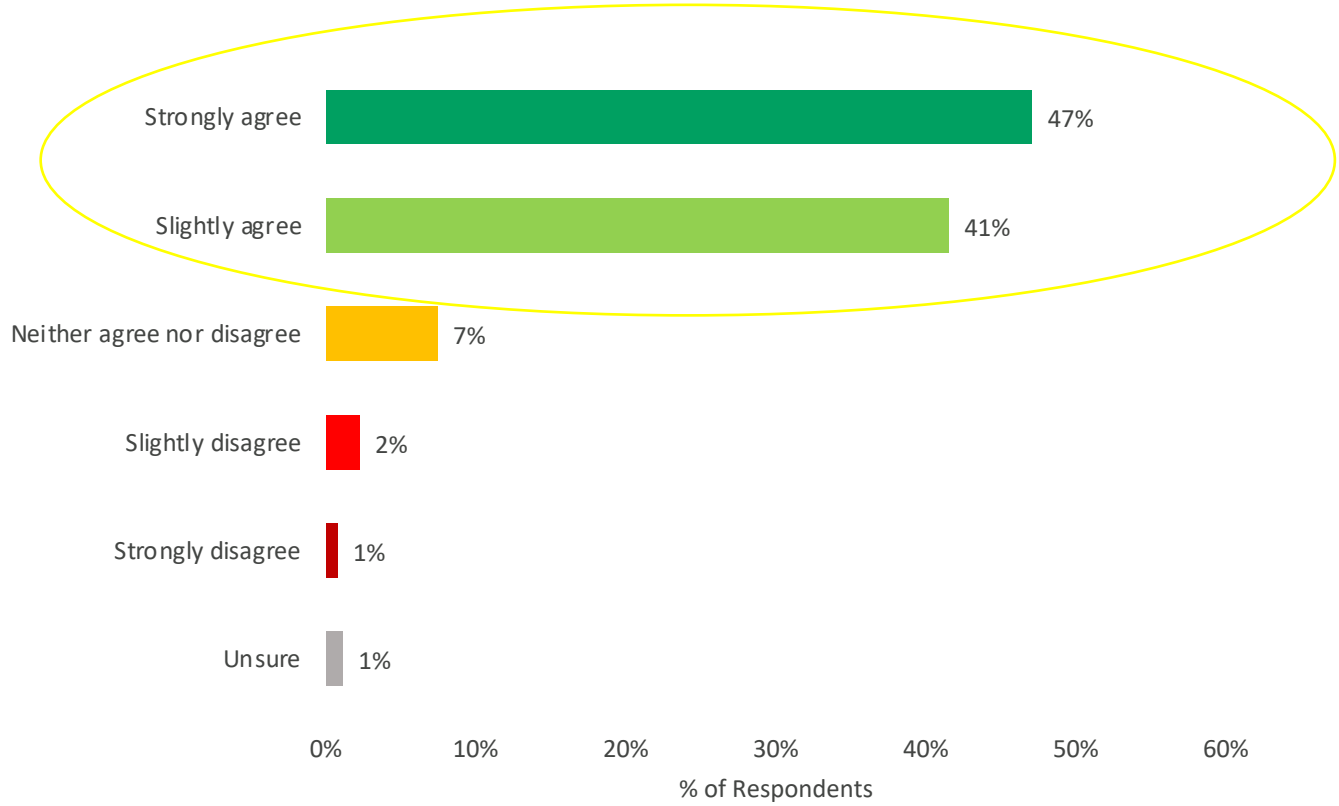
Q3. To what extent do you agree with the following statement: "Only biosimilars that have been individually evaluated specifically for the impact of switching on safety and efficacy should be deemed interchangeable." (n=270)



- 85% of respondents agreed that only biosimilars that have been individually evaluated specifically for the impact of switching on safety and efficacy should be deemed interchangeable.

Biosimilar Switching Studies' Effects on Confidence in Safety

*Q4. To what extent do you agree with the following statement: "Biologics are complex medicines that can cause unwanted immune responses in patients; biosimilar switching studies **increase my confidence** in the safety of moving my patients from an originator medicine to the biosimilar that has been studied and determined to be interchangeable with the originator." (n=270)*



- 88% of respondents agreed that biosimilar switching studies increase their confidence in the safety of moving their patients from an originator medicine to the biosimilar that has been studied and determined to be interchangeable with the originator.

Dr. McKibbin Op-Ed: Altoona Mirror (October 27, 2024)

Altoona Mirror

Lower med standards endangers health

Local voices

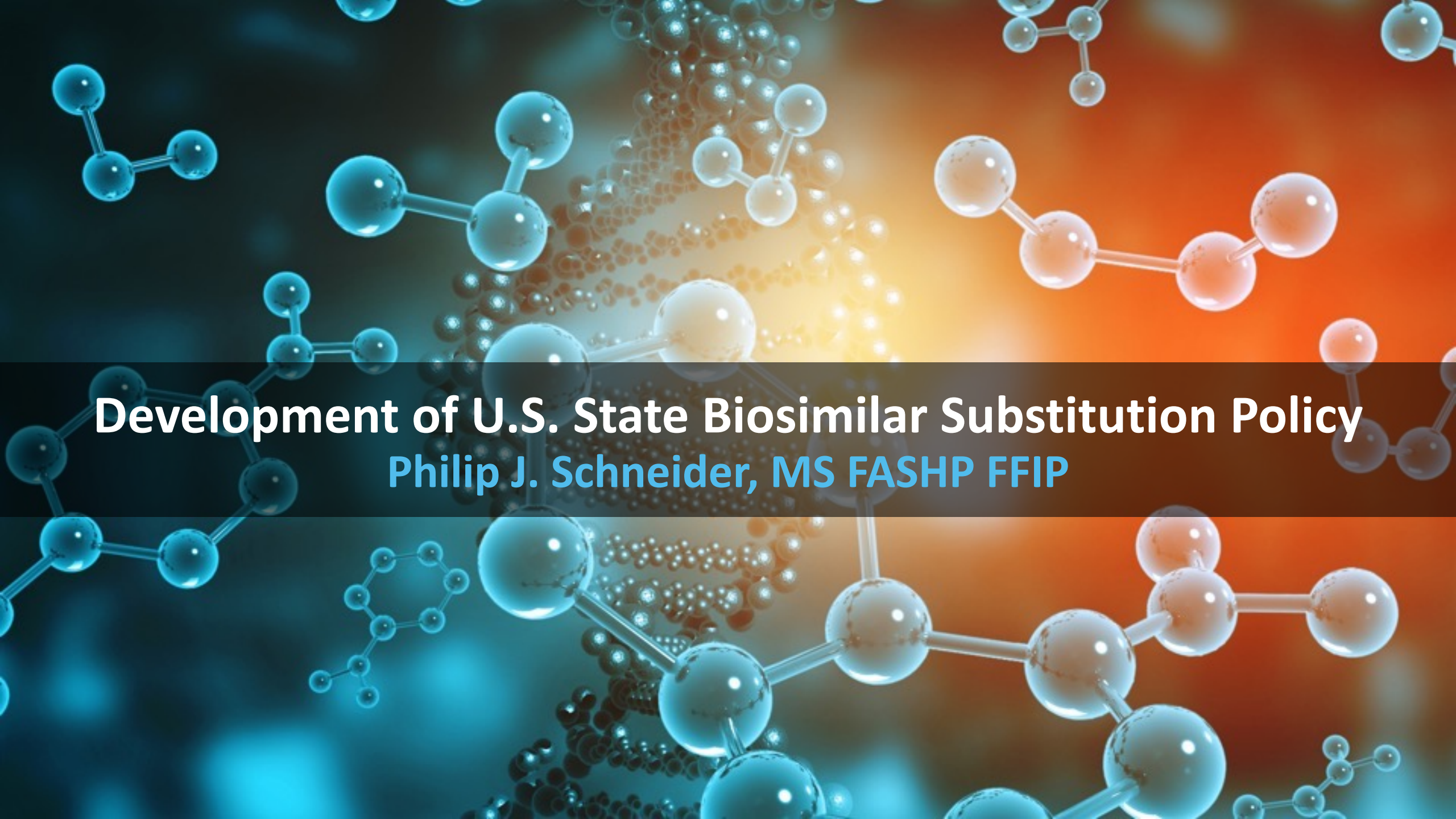
As a practicing physician in Pennsylvania, I firmly believe that the relationship between a doctor and their patient should guide every treatment decision.

When physicians recommend treatments, we rely on years of training, clinical evidence, and the unique medical history of each patient.

Patients should have the confidence to make decisions about their care in partnership with their doctor, without the fear that insurance companies or pharmacies will override those choices for non-medical reasons such as increasing profitability.

Unfortunately, a proposed policy change threatens to undermine this relationship and could disrupt the treatment stability of patients across Pennsylvania.

Biologic medications are commonly prescribed to treat conditions like cancer, arthritis and Crohn's disease — serious chronic conditions that require careful management. "Biosimilars," which are designed to mimic these biologic medications, help create competition and lower costs.

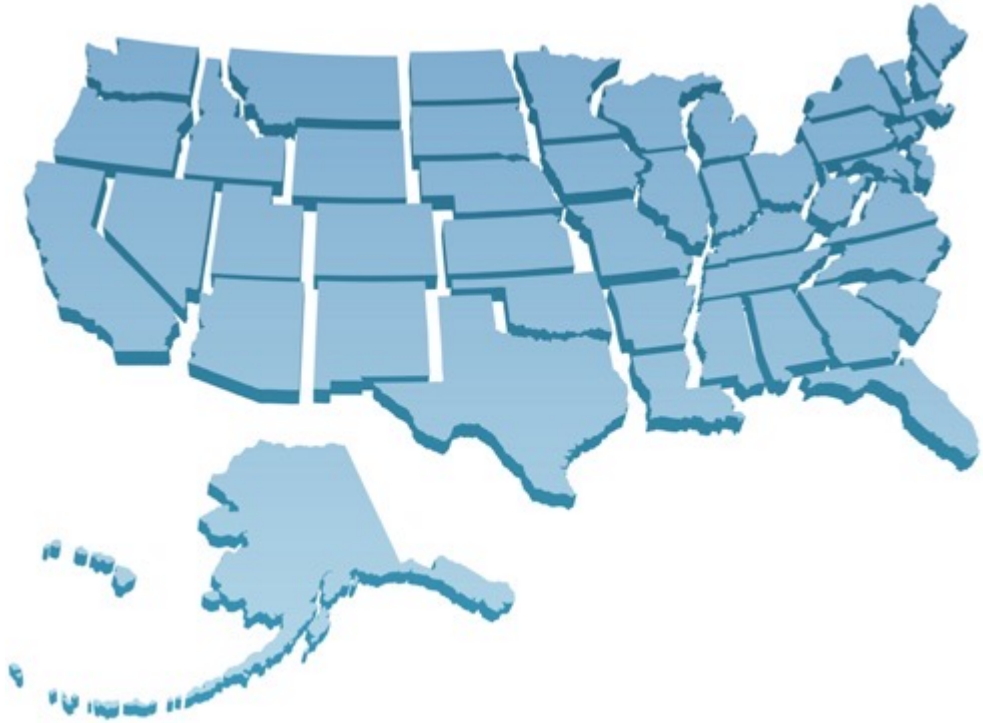


Development of U.S. State Biosimilar Substitution Policy

Philip J. Schneider, MS FASHP FFIP

U.S. States Control Pharmacy Substitution

- **Each of the 50 states' Pharmacy Practice Acts needed to be updated.**
- Collaboration and compromise were necessary between many stakeholders including physicians, pharmacists, insurers, patient groups, and manufacturers.
- The final laws reflected this negotiated compromise and were **widely supported by state medical societies.**

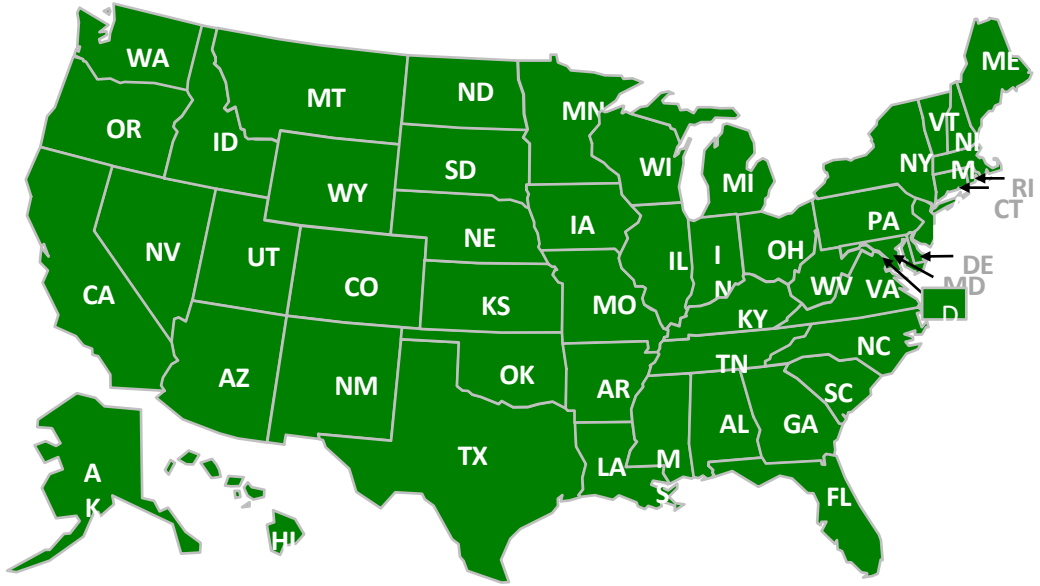


FACT CHECK: European Policies Generally Preserve Physician Control of Treatment Decisions… and Forbid Automatic Substitution

- Physicians are free to choose between all available products, including originator and biosimilars. Some countries encourage starting patients on the lowest cost product, often a biosimilar.
- The decision to switch to a biosimilar is made by the physician.
- In nearly every Western European country, automatic substitution of biosimilars at the pharmacy level is forbidden.

Automatic Substitution Legislation, 2013-2021

- **ASBM and its members worked for 8 years across 50 states in support of the legislation.**
- **Physicians were initially reluctant to support ANY automatic substitution of biologics.**
- **Pharmacists felt notification requirements were onerous.**



KEY FEATURES OF AGREED-UPON LEGISLATION:

- **Only INTERCHANGEABLE BIOSIMILARS will be automatically substituted.**
- **Physicians are able to prevent a substitution they feel is inappropriate (DAW)**
- **Pharmacists must communicate to physicians within 3-5 days that a substitution has occurred (maintain accurate patient record).**
- **Patient notification required in many states.**

States Recognize the Difference Between Interchangeable and Non-Interchangeable Biosimilars and Can Amend Their Own Laws if the So Choose.

- **2023 Prescription Drug Advisory Board (PDAB) Recommendation (Oregon)**

- **Recommends Legislature add language permitting a (non-interchangeable) biosimilar to be substituted,** where previously only an "interchangeable biosimilar" could be substituted.

https://dfr.oregon.gov/pdab/Pages/public-comment.aspx


Regulatory Perspective
Michael Reilly, Esq.

U.S. Senate Bill 2035 Biosimilar Red Tape Elimination Act

Lee Seeks Increased Competition in Biological Drug Market

July 13, 2023

WASHINGTON - Sens. Mike Lee (R-UT), Ben Ray Lujan (D-NM), Mi
Red Tape Elimination Act to increase competition within the biolo
drugs.

For small-molecule drugs, pharmacists can substitute generics in
to increasing competition and bringing down the cost of prescrip

The generic equivalent of a biological drug is known as a biosimilar. Unlike generic drugs, many states will not allow pharmacists to substitute a biosimilar unless the FDA declares it to be “interchangeable.”

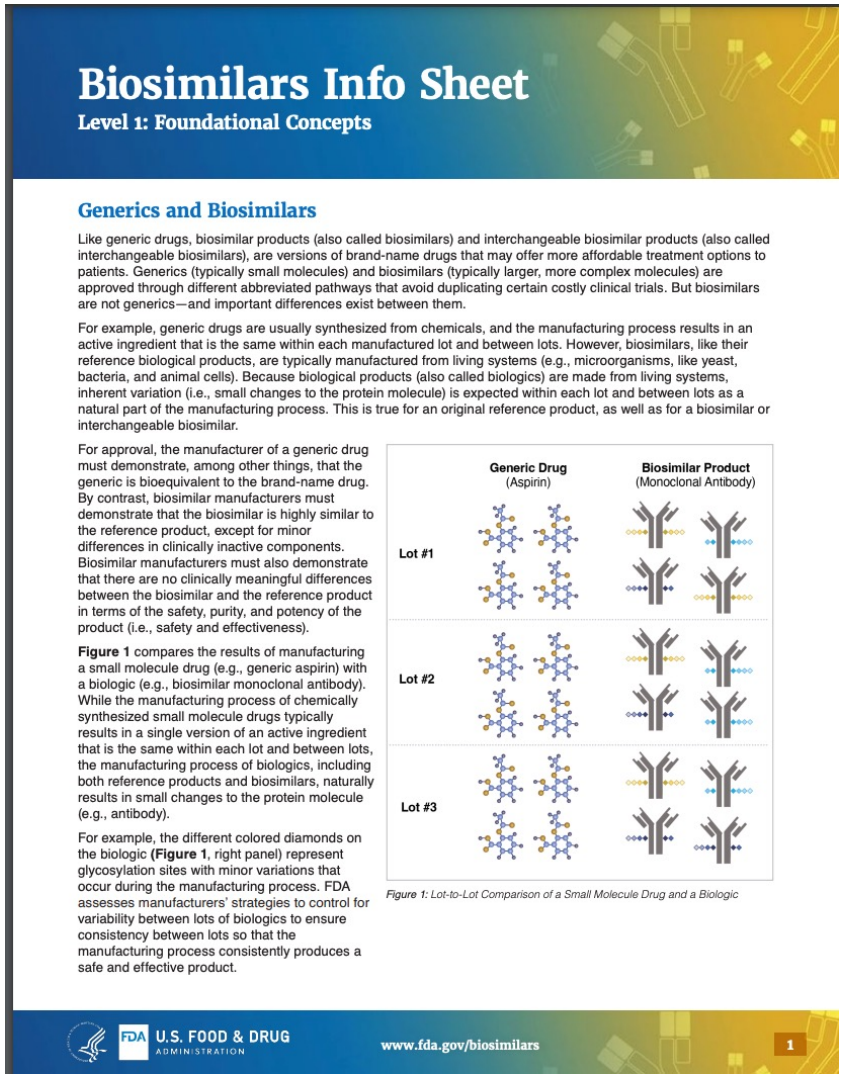
The generic equivalent of a biological drug is known as a biosimilar. Unlike generic drugs, many states will not allow pharmacists to substitute a biosimilar unless the FDA declares it to be “interchangeable.” The current process is cumbersome and expensive.

Under current regulations, acquiring interchangeable status requires the product to undergo switching studies - whereby participants must alternate between the biologic and the biosimilar – over and above the initial approval as a biosimilar. These studies can cost millions of dollars and further delay market access. After examining 15 years of data, the European Medicines Agency (EMA)

FACT CHECK: FDA Says Biosimilars are NOT Generics

"**But biosimilars are not generics**—and important differences exist between them."

-FDA Biosimilars Info Sheet



Biosimilars Info Sheet

Level 1: Foundational Concepts

Generics and Biosimilars

Like generic drugs, biosimilar products (also called biosimilars) and interchangeable biosimilar products (also called interchangeable biosimilars), are versions of brand-name drugs that may offer more affordable treatment options to patients. Generics (typically small molecules) and biosimilars (typically larger, more complex molecules) are approved through different abbreviated pathways that avoid duplicating certain costly clinical trials. But biosimilars are not generics—and important differences exist between them.

For example, generic drugs are usually synthesized from chemicals, and the manufacturing process results in an active ingredient that is the same within each manufactured lot and between lots. However, biosimilars, like their reference biological products, are typically manufactured from living systems (e.g., microorganisms, like yeast, bacteria, and animal cells). Because biological products (also called biologics) are made from living systems, inherent variation (i.e., small changes to the protein molecule) is expected within each lot and between lots as a natural part of the manufacturing process. This is true for an original reference product, as well as for a biosimilar or interchangeable biosimilar.

For approval, the manufacturer of a generic drug must demonstrate, among other things, that the generic is bioequivalent to the brand-name drug. By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of the safety, purity, and potency of the product (i.e., safety and effectiveness).

Figure 1 compares the results of manufacturing a small molecule drug (e.g., generic aspirin) with a biologic (e.g., biosimilar monoclonal antibody). While the manufacturing process of chemically synthesized small molecule drugs typically results in a single version of an active ingredient that is the same within each lot and between lots, the manufacturing process of biologics, including both reference products and biosimilars, naturally results in small changes to the protein molecule (e.g., antibody).

For example, the different colored diamonds on the biologic (**Figure 1**, right panel) represent glycosylation sites with minor variations that occur during the manufacturing process. FDA assesses manufacturers' strategies to control for variability between lots of biologics to ensure consistency between lots so that the manufacturing process consistently produces a safe and effective product.

Figure 1: Lot-to-Lot Comparison of a Small Molecule Drug and a Biologic

https://www.help.senate.gov/imo/media/doc/66f88c64-f619-00bb-f6f5-075a1b4248f2/S.2305%20MA.pdf

Lee Seeks Increased Competition in Biological Drug Market

July 13, 2023

WASHINGTON - Sens. Mike Lee (R-UT), Ben Ray Lujan (D-NM), Mike Braun (R-IN), and J.D. Vance (R-OH) introduced the Biosimilar Red Tape Elimination Act to increase competition within the biological drug market and increase access to low-cost prescription drugs.

For small-molecule drugs, pharmacists can substitute gener ential to increasing competition and bringing down the cost of pres

The generic equivalent of a biological drug is known as a bio sts to substitute a biosimilar unless the FDA declares it to be "inter

After examining 15 years of data, the European Medicines Agency (EMA) recently stated that switching studies are unnecessary for biosimilars to obtain interchangeable status.

Under current regulations, acquiring interchangeable status requires the product to undergo switching studies - whereby participants must alternate between the biologic and the biosimilar – over and above the initial approval as a biosimilar. These studies can cost millions of dollars and further delay market access. After examining 15 years of data, the European Medicines Agency (EMA)

Fact Check: "Interchangeable": Different Meaning in U.S. and Europe

- **The European use means "substitutable by the prescriber"**
- **In the U.S., as in Europe, ALL BIOSIMILARS are substitutable by the prescriber.**
- **The U.S. "interchangeable biosimilar" category refers to biosimilars that are also substitutable by a pharmacist, due to having provided additional data to FDA showing that switching to the biosimilar will not impact the safety or efficacy for the patient.**
- **Automatic pharmacy substitution of biosimilars in Europe is rare, and often banned.**

https://safebiologics.org/wp-content/uploads/2023/11/ IC-EUvsUS-FNL.pdf

Not "Cutting Red Tape":

Deeming ALL Biosimilars INTERCHANGEABLE without additional data- treating them as generics

Restricting FDA's ability to request data for scientific determinations in interchangeable biosimilar approvals

Circumventing limits placed on automatic substitution by laws passed in 50 states.

https://www.help.senate.gov/imo/media/doc/66f88c64-f619-00bb-f6f5-075a1b4248f2/S.2305%20MA.pdf

Shown Here:
Introduced in Senate (07/13/2023)

118TH CONGRESS
1ST SESSION

S. 2305

To improve the requirements for making a determination of interchangeability of a biological product and its reference product.

IN THE SENATE OF THE UNITED STATES

JULY 13, 2023

Mr. LEE (for himself, Mr. LUJÁN, Mr. BRAUN, and Mr. VANCE) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

A BILL

To improve the requirements for making a determination of interchangeability of a biological product and its reference product.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Biosimilar Red Tape Elimination Act".

SEC. 2. BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) IN GENERAL.—Section 351(k) of the Public Health Service Act (42

(1) in the subsection heading, by striking "OR INTERCHANGEABLE";

" To improve the requirements for making a determination of interchangeability of a biological product and its reference product."

Nothing in this bill IMPROVES the requirements for making a determination of interchangeability.

In fact, it does the exact opposite…

Summary (1) | Text (1) | Actions (1) | Titles (2) | Amendments (0) | Cosponsors (4) | Committees (1) | Related Bills (0)

Summary: S.2305 — 118th Congress (2023-2024)

Listen

There is one summary for S.2305. Bill summaries are authored by CRS.

Shown Here:
Introduced in Senate (07/13/2023)

Biosimilar Red Tape Elimination Act

This bill removes certain requirements for biosimilars to be designated as interchangeable. (Biosimilars that are designa
new prescription, depending on state pharmacy laws.)

Specifically, the bill establishes a presumption that an approved biosimilar is interchangeable with the reference product
exclusivity periods for a first interchangeable biosimilar (i.e., a product that is the first interchangeable biosimilar to be ap

The Food and Drug Administration (FDA) may require a manufacturer of a biosimilar to conduct a safety study with resp
the FDA briefs certain members of specified congressional committees to explain why the study is necessary.

CONGRESS.GO

This bill removes certain requirements for biosimilars to be designated as interchangeable. (Biosimilars that are designated as interchangeable may be substituted for the reference product at a pharmacy without a new prescription, depending on state pharmacy laws.)

Specifically, the bill establishes a presumption that an approved biosimilar is interchangeable with the reference product without the need for additional evidence from the manufacturer, and it removes the applicable exclusivity periods for a first interchangeable biosimilar (i.e., a product that is the first interchangeable biosimilar to be approved with respect to the reference product).

The Food and Drug Administration (FDA) may require a manufacturer of a biosimilar to conduct a safety study with respect to switching or alternating between the biosimilar and the reference product, but only after the FDA briefs certain members of specified congressional committees to explain why the study is necessary.

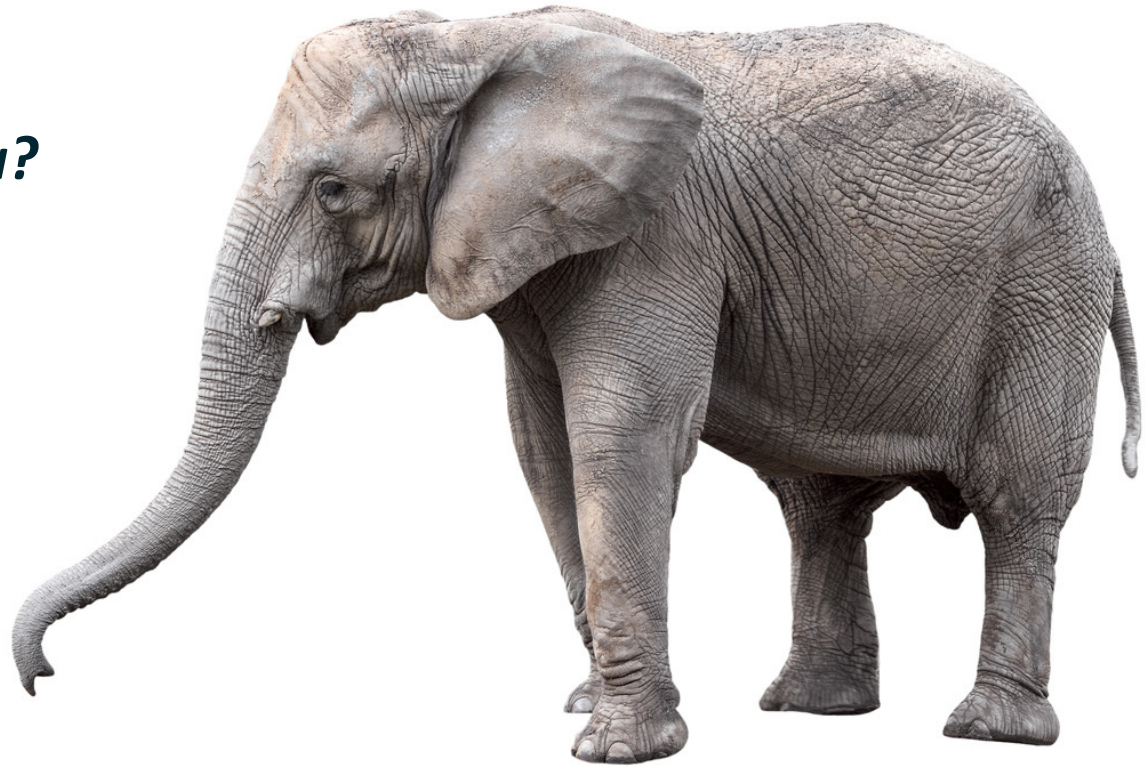
https://www.govtrack.us/congress/bills/118/s2305/text


I DEEM YOU
INTERCHANGEABLE!

Elephant in the Room: 2 Questions

1. Doesn't the fact that FDA is supporting this mean it is a good idea?

2. Why is there no opposition from physician groups?




Why is the FDA Supporting Legislation
That Strips Its Discretionary Authority?

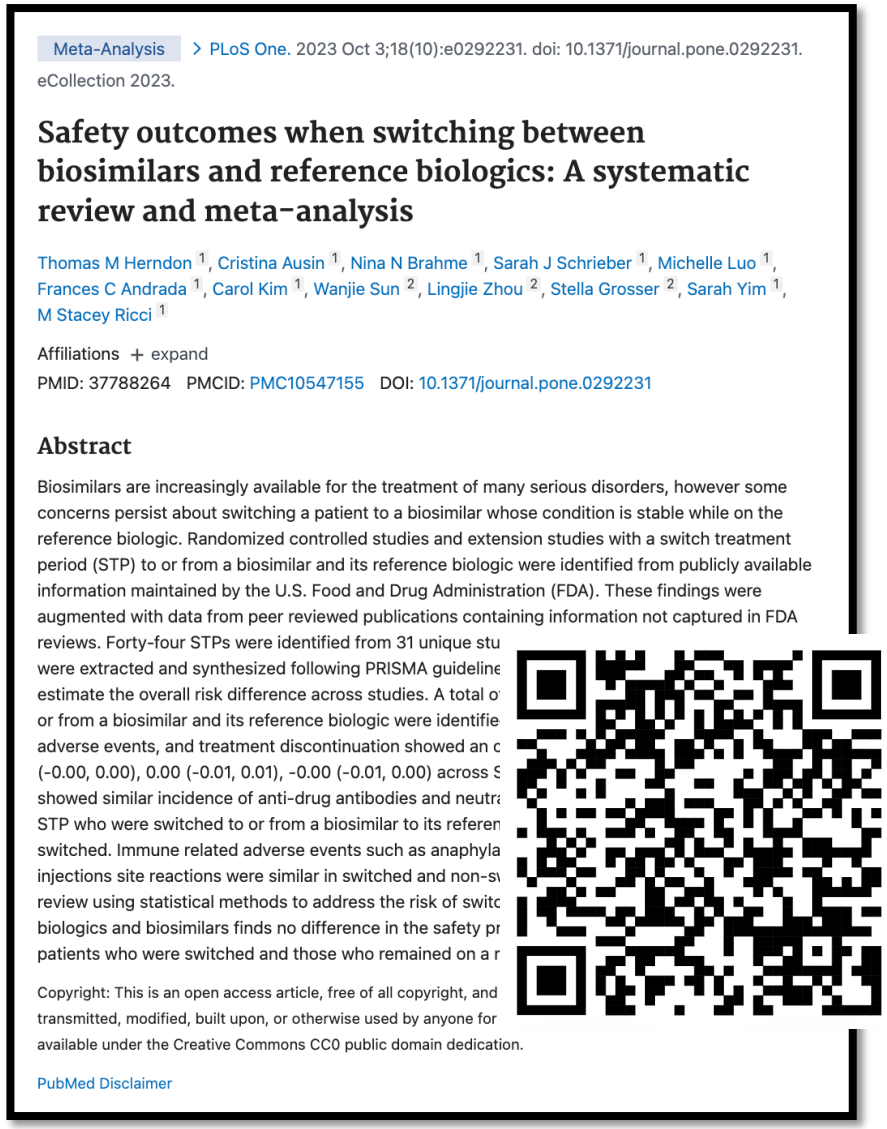
FDA Meta-Analysis Paper (October 2023)

Support largely rests on one -analysis:

"Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis" (October 2023, Herndon et al)

- **Cited by proponents of applying generics-style substitution paradigm to biosimilars.**
- **Cited in June 2024 FDA Draft Guidance de-emphasizing importance of switching studies for interchangeability**
- Claims "insignificant risk" of safety or efficacy issues from switching between reference and biosimilar products.

https://pubmed.ncbi.nlm.nih.gov/37788264/



Meta-Analysis > PLoS One. 2023 Oct 3;18(10):e0292231. doi: 10.1371/journal.pone.0292231. eCollection 2023.

Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis

Thomas M Herndon [1], Cristina Ausin [1], Nina N Brahme [1], Sarah J Schrieber [1], Michelle Luo [1], Frances C Andrada [1], Carol Kim [1], Wanjie Sun [2], Lingjie Zhou [2], Stella Grosser [2], Sarah Yim [1], M Stacey Ricci [1]

Affiliations + expand

PMID: 37788264 PMCID: PMC10547155 DOI: 10.1371/journal.pone.0292231

Abstract

Biosimilars are increasingly available for the treatment of many serious disorders, however some concerns persist about switching a patient to a biosimilar whose condition is stable while on the reference biologic. Randomized controlled studies and extension studies with a switch treatment period (STP) to or from a biosimilar and its reference biologic were identified from publicly available information maintained by the U.S. Food and Drug Administration (FDA). These findings were augmented with data from peer reviewed publications containing information not captured in FDA reviews. Forty-four STPs were identified from 31 unique stu
were extracted and synthesized following PRISMA guideline
estimate the overall risk difference across studies. A total o
or from a biosimilar and its reference biologic were identifie
adverse events, and treatment discontinuation showed an c
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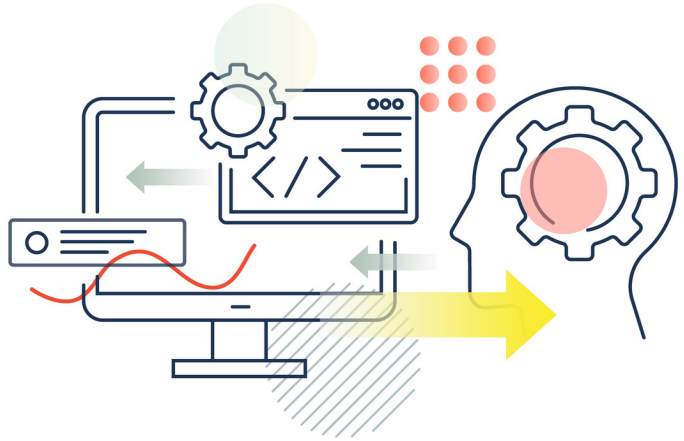
Meta Analyses: Why Are They Controversial?



Criticisms and Disadvantages:

- **Quality of Included Studies**: Dependence on the quality of included studies can amplify existing flaws.
- **Heterogeneity**: Variability in study designs and populations may hinder valid conclusions.
- **Publication Bias**: Overrepresentation of studies with positive results skews overall findings.
- **Selection Bias**: Subjective choices in study selection can introduce bias.
- **Data Overlap**: Inclusion of duplicated data can distort results.
- **Apples to Oranges**: Combining dissimilar studies can lead to inappropriate conclusions.
- **Statistical Issues**: Choices in statistical modeling can significantly influence outcomes.
- **Oversimplification**: Potential to obscure complex details and variations between studies.
- **Conflicts of Interest**: Biases due to researchers' affiliations or beliefs can affect outcomes.
- **Overinterpretation**: Results may be viewed as definitive when they are only part of the evidence.

ASBM Whitepaper Raises Concerns About Using Meta-Analysis

Concerns Raised by McKibbin and Reilly:

- **Highly selective and limited analysis.** Only 44 randomized controlled trials and their extension studies

- **Efficacy Impacts Not Evaluated, only Safety**
  Note: FDA regulatory approval for interchangeable biosimilar products is based on demonstrating that neither safety nor treatment efficacy are negatively affected.

- **Inappropriate Pooling of Data** from studies across therapeutic areas- not grouped by individual therapies, indications, or by the number of switches.

- **Extrapolates Multi-Switch Safety from Largely Single-Switch Studies:** 64% were single-switch studies.

- **Neglects Real World Considerations of Patient Variability**

GaBiJournal
Generics and Biosimilars Initiative Journal

PERSPECTIVE

Misinformation about interchangeable biosimilars: undermines US health policy, physician confidence, and patient health

Michael S Reilly, Esq; Ralph D McKibbin, MD, FACP, FACG, AGAF

The US biosimilar program has been highly successful with 53 biosimilars approved by the US Food and Drug Administration (FDA) for 17 reference products. As in most advanced nations of Europe, all FDA-approved biosimilars may be substituted in place of the reference product by the physician. To be substitutable at the pharmacy level. However, US state law requires these to be FDA-approved as 'interchangeable biosimilars'– a designation earned through additional data showing no loss of safety or efficacy is expected even after multiple switches, relative to a patient who remained on the reference product. Thirteen biosimilars have earned this designation. FDA currently has the flexibility to determine how these data requirements are met; this can include switching studies, however, multiple interchangeable biosimilars have been approved without them. This data-driven approach has significantly bolstered physician and patient confidence in biosimilar safety and efficacy, particularly regarding pharmacy substitution. Yet there has recently been a push by policymakers at many levels of government to limit the types of data the FDA can consider, or otherwise lower the data requirements.
The authors critically examine a meta-analysis frequently cited by policymakers supportive of these efforts. They argue that the study's conclusions – and the policy proposals – are unsupported by the data, which do not address efficacy impacts and extrapolate multi-switch safety despite a disproportionate reliance on single-switch studies. Rushing to dismantle proven standards based on these and other misconceptions, the authors argue, poses a potential risk to patient treatment stability and confidence in biosimilars. Preserving the quality standards that have defined the introduction of interchangeable biosimilars in the US, and the FDA's flexibility to seek additional data when needed, will help ensure that patient care remains personalized and the integrity of the patient–physician relationship is maintained.

Keywords: Biosimilarity, interchangeability, regulation, uptake

Introduction
Biosimilars are safe and effective drugs designed to be cost-effective alternatives to higher-priced branded biologicals. However, biosimilars are not identical to their reference biologicals. While generic substitution for chemically derived small molecule drugs is a long-standing, uncontroversial practice, the substitution of non-identical biosimilars for branded biologicals is of concern to physicians and patients [1-4] for many reasons, including the potential risk to patient safety.

Despite these concerns, recent policies have been proposed that would shift the substitution practices for non-identical biosimilar products to follow substitution practices for identical generic molecules for their reference products. Furthermore, these polices are blurring the distinction between biosimilars and 'interchangeable biosimilars', to the potential detriment of patients. This may have unintended consequences for patients that policymakers need to consider when proposing biosimilar legislation.

Today, to earn the designation of interchangeable biosimilar, manufacturers must provide additional data demonstrating with near certainty that the biosimilar product will produce the same clinical result as the reference product in any given patient, and for a product administered more than once, that the risk of switching between a reference product and an interchangeable biosimilar must not be greater than the risk of using the reference product without switching [5]. The US Food and Drug Administration (FDA) has great flexibility regarding what data is required to make this determination; it may or may not require switching studies, for example. As of June 2024, 53 biosimilars approved by FDA, 13 have met the standards for interchangeability [6], with more seeking this designation. While all US biosimilars are substitut-
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tution by a third party per se. However, third-party biosimilar substitution raises a variety of issues pertaining to patient and physician consent, maintenance of accurate patient records, clear product identification and traceability, adequate pharmacist education, and clear communication between healthcare providers. While US physicians have historically expressed these concerns when surveyed [8] biosimilar substitution practices; they have also specifically expressed concern with the potential impact of medication switches on patient stability [1-4]. Treatment plans are tailored to individual

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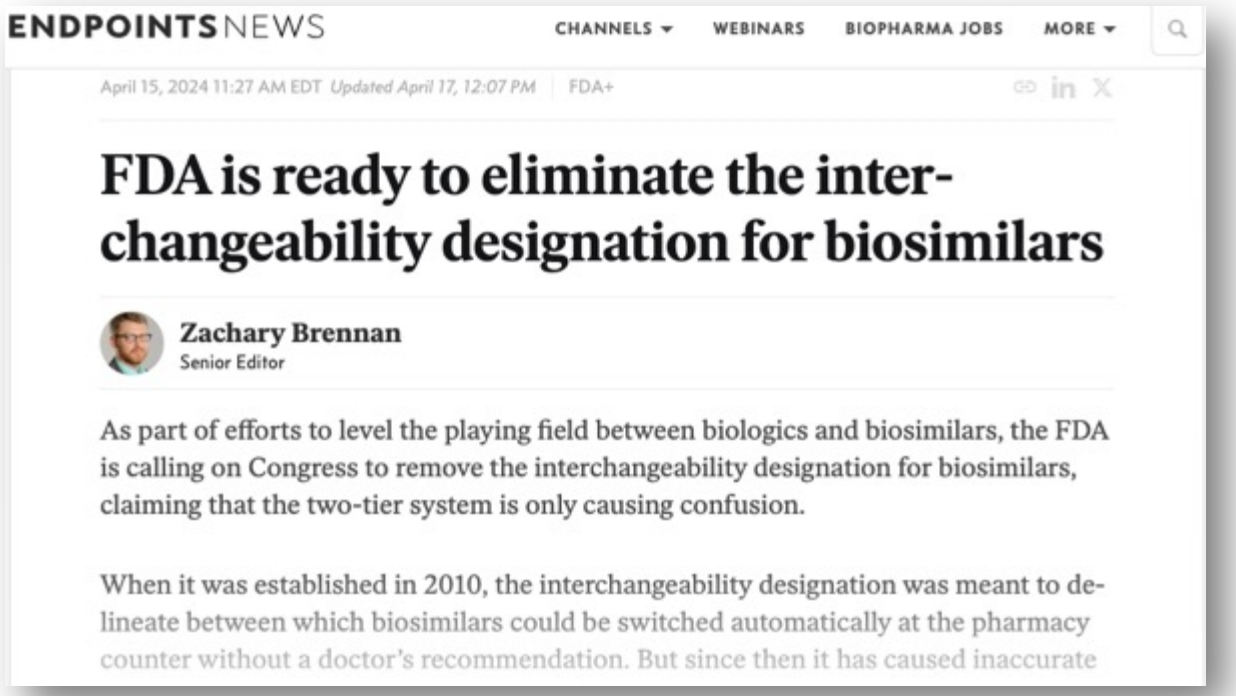
https://pubmed.ncbi.nlm.nih.gov/37788264/

April 2024 EndpointsNews Interview with FDA Official

- Sarah Yim, director of the FDA's Office of Therapeutic Biologics and Biosimilars called upon Congress to eliminate the regulatory distinction between interchangeable and non-interchangeable biosimilars.
- Yim said the shift is necessary now **because there are no longer any scientific or clinical reasons** to make a difference between "the two classes of products, because instead of having two different levels of similarity, for example, we don't feel like we can implement that," Yim said.



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April 15, 2024 11:27 AM EDT *Updated April 17, 12:07 PM* | FDA+

FDA is ready to eliminate the inter-changeability designation for biosimilars

Zachary Brennan
Senior Editor

As part of efforts to level the playing field between biologics and biosimilars, the FDA is calling on Congress to remove the interchangeability designation for biosimilars, claiming that the two-tier system is only causing confusion.

When it was established in 2010, the interchangeability designation was meant to de-lineate between which biosimilars could be switched automatically at the pharmacy counter without a doctor's recommendation. But since then it has caused inaccurate

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Thursday, October 31, 2024

FDA Drug Center Officials Defend Biosimilar Switching Policy Change

By Jessica Karins / October 21, 2024 at 10:39 AM

"Accumulated scientific evidence has led FDA to conclude **clinical studies are <u>mostly unnecessary</u>** to determine whether a biosimilar drug should be interchangeable with its reference product"

"FDA's accrued experience with switching between reference products and biosimilars, and global post-approval data, have not demonstrated clinical concerns with the practice; the officials say this provides support for the idea that **a switching study is not necessary <u>in most cases</u>."**

"we were able to **approve the majority (9/13) of interchangeable products** without the need for a clinical switching study"

Inside Health Policy: October 21, 2024 (Continued)

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Thursday, October 31, 2024

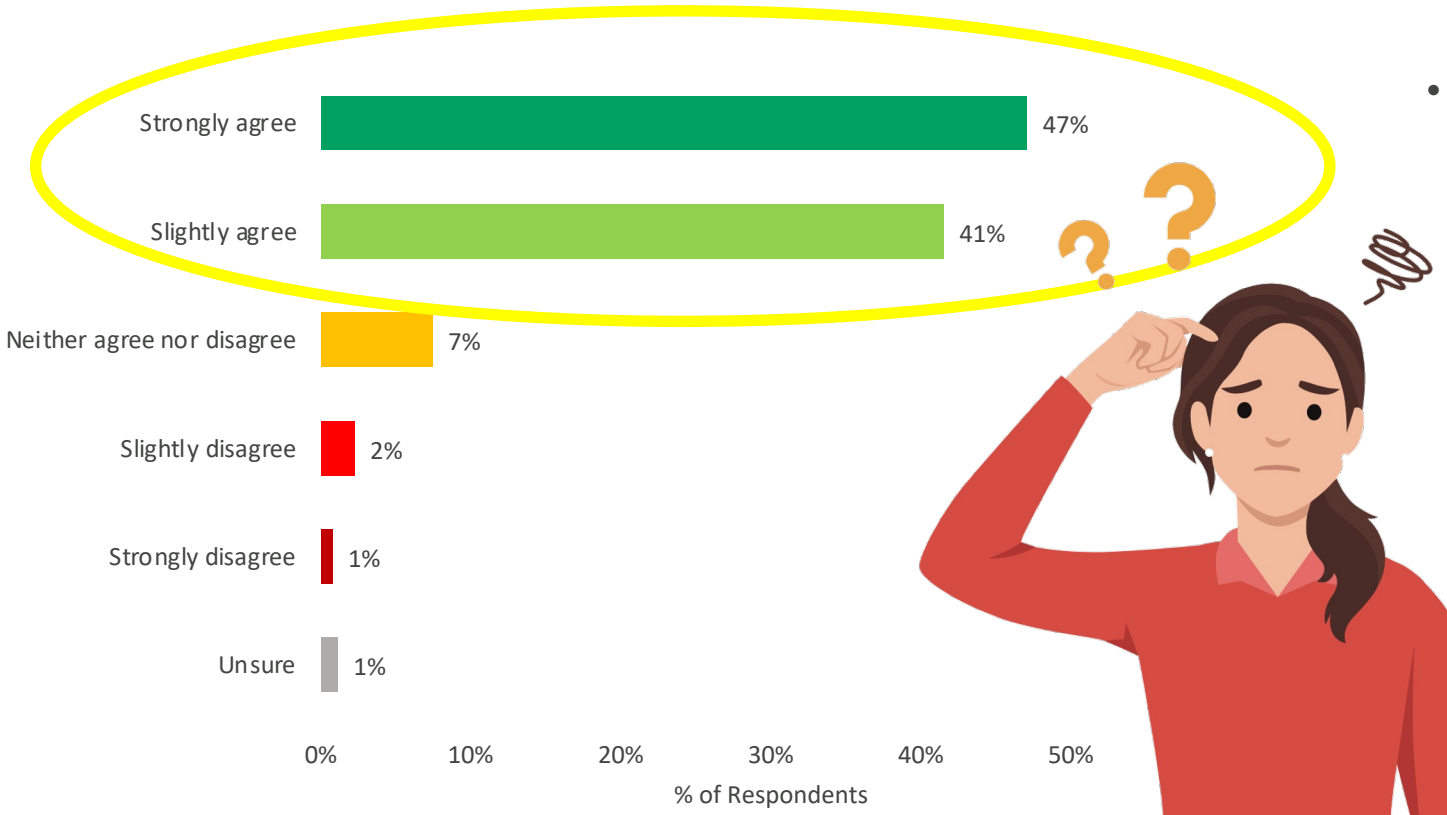
FDA Drug Center Officials Defend Biosimilar Switching Policy Change

By Jessica Karins / October 21, 2024 at 10:39 AM

- The Association for Accessible Medicines (AAM) told *Inside Health Policy* that the interchangeability bill has bipartisan support and is a policy supported by FDA, the Federal Trade Commission and state governments.
- The bill's original bipartisan cosponsors, who included Sen. JD Vance (R-OH), now the Republican nominee for vice president, said **the change to eliminate additional interchangeability studies would increase patient and provider confidence in biosimilars and mean lower prices for patients.**

Biosimilar Switching Studies' Effects on Confidence in Safety

*Q4. To what extent do you agree with the following statement: "Biologics are complex medicines that can cause unwanted immune responses in patients; biosimilar switching studies **increase my confidence** in the safety of moving my patients from an originator medicine to the biosimilar that has been studied and determined to be interchangeable with the originator." (n=270)*



- 88% of respondents agreed that biosimilar switching studies increase their confidence in the safety of moving their patients from an originator medicine to the biosimilar that has been studied and determined to be interchangeable with the originator.

The FDA is Not Infallible

Example: Recent FDA Reversal on Shortage/Compounding of GLP-1 Drugs

FDA retreats from declaring end to Mounjaro shortage

Alexandra Murphy - Monday, October 21st, 2024

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In a reversal, the FDA is reconsidering its decision to end the shortage status of tirzepatide, after a recent lawsuit and intense public pressure, *The Washington Post* reported Oct. 21.

The move allows compounding pharmacies to temporarily resume selling cheaper, unbranded versions of the drugs while the FDA continues to assess whether a shortage exists. The FDA's shift follows widespread confusion among patients and pharmacies, with many patients unable to afford the branded drugs and relying on the compounded versions.

After the FDA initially declared the shortage over on Oct. 2, compounding pharmacies were forced to stop production, leading to panic among patients who depend on these drugs for weight management.

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FDA Reversal on Knockoff GLP-1 Drugs Brings Confusion, and Few Answers

Story by Josh Nathan-Kazis • 2w • 3 min read

Review

- Flawed legislation founded on two false premises:
  - That biosimilars are generics – they're not
  - That this policy would align us with Europe, where automatic pharmacy substitution of biosimilars is rare and often banned
- Supported by a weak study with **flawed methodology**
- Physicians when informed overwhelmingly oppose the bill's intent (deeming all biosimilars interchangeable).
- Its primary supporters are **payers**

Supporters/Beneficiaries of S.2305

PCMA

PBM Industry Trade Group

ERIC
THE ERISA INDUSTRY COMMITTEE
Shaping benefit policies before they shape you.

ERISA Industry Committee
(Large, Self-Insured Employers)

Conclusion

- Conversation on Capitol Hill is about how the proposed savings can be used to “pay for” other programs.
- **We should not be bartering and horse-trading where patient safety is involved.**

Patient Perspective

Andrew Spiegel, Esq.


SafeBiologics
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GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments
PANEL DISCUSSION

Additional Resources About Interchangeable Biosimilars

ASBM Fact Sheet on Biosimilar Red Tape Elimination Act (S.2305)

Interchangeable Biosimilars: Europe and the U.S.

ASBM Whitepaper Response to Meta-Analysis

ASBM Letter to BRTEA (s.2305) Sponsor & Co-sponsor

ASBM Physician Survey (2024)

Op-ed: Congress Should Maintain Current FDA Standards (Michael Reilly)


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