III. Prescribing and Switching

How Do Different Countries Approach Biosimilar Substitution?

Is “Automatic Substitution” Permitted?

Western Europe: Automatic Substitution is Extremely RARE.

- **In the vast majority of European countries, treatment decisions, including the decision to switch to a biosimilar, rests with physician/patient.**
- **Physicians are often encouraged to prescribe lower-cost products to new patients.**
- **The payer continues to reimburse for multiple products.** This ensures a **robust and sustainable biosimilar market with multiple suppliers in a given product class.**
- Even in Norway with a national tendering system, physicians retain the prescription choice among all available products but are strongly encouraged to choose the lowest priced product for new (naive) patients.
- Only Denmark, following a transparent national tender process, will solely reimburse the winning product, except in rare substantiated circumstances.
- **No European country has stopped reimbursement of an originator product through an arbitrary government fiat.**

Automatic Substitution in Eastern Europe: Permitted

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

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

POLAND: Permitted, pharmacists are to discuss with patient.

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

Three Countries Whose Policies We Will Examine More Closely

CANADA:

- Leaves automatic substitution decisions to PROVINCES.
  2 have implemented, and 2 more have announced **MANDATORY SWITCHING policies.**

AUSTRALIA:

- **Permits automatic substitution** (“a-flagging”) of biosimilars.
- Physicians can prevent substitution (“Brand Substitution Not Permitted.”)

US:

- All 50 STATES permit **automatic substitution of “INTERCHANGEABLE” Biosimilars (higher data requirement).**
- Physicians can prevent substitution (“Dispense As Written”, DO Not Substitute, etc.)
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How Important is Communication of a Biosimilar Substitution?

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

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

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

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

How Important is “Dispense as Written” (DAW) Authority?

80% *of Canadian physicians consider it “very important” or “critical”*

74% *of EU physicians consider it “very important” or “critical”*

82% *of US physicians consider it “very important” or “critical”*

85% *of Latin American physicians consider it “very important” or “critical”*

What is Non-Medical Switching?

Switching a patient's medicine, often by a third party such as a government or private payer, for reasons other than that patient's health and safety.

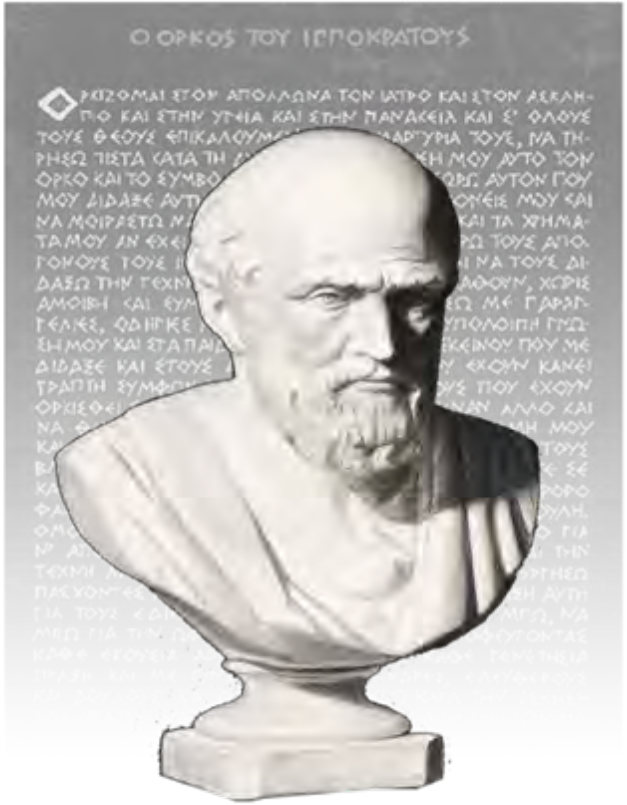
(e.g. greater profits, controlling costs, more efficient use of limited resources, etc.)

Issues Surrounding Non-Medical Switching with Biologics

- Changing treatment may change the control a patient has over their condition.
- Patient and doctor often believe they should have the final say about treatment choices- which biologic to use, and if and when switching is appropriate.
- If your medicine is working for you, most doctors don't think it is a good idea to switch from one biologic to another for cost reasons only.

Physicians Are Generally Cautious About Switching

- Clinicians by nature and training are generally conservative regarding treatments and are hesitant to change without sufficient experience, clinical data and independent recommendations.
- They are not comfortable with non-medical switching, especially with patients who are doing well on a particular therapy.



Hippocratic Oath: "first, do no harm"

Non-Medical Switching: Private Insurer

- Health insurers may encourage a change from a biologic to a non-interchangeable biosimilar, for the sole reason of reducing costs.

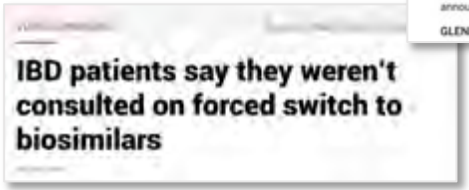
- No patient protections exist to prevent insurers from forcing a patient to switch therapies:
  - Higher out of pocket costs (coinsurance, copay, etc.) for your current therapy
  - Formulary design changes mid-plan year and plan-year to plan-year
  - Disadvantage products by changing tiers
  - Blocking the use of co-pay cards

- Some data suggests that Non-Medical Switching may actually increase costs for the individual and the health care system because of an increase in hospitalizations, doctor visits and other health care services.

Non-Medical Switching: Government Payer

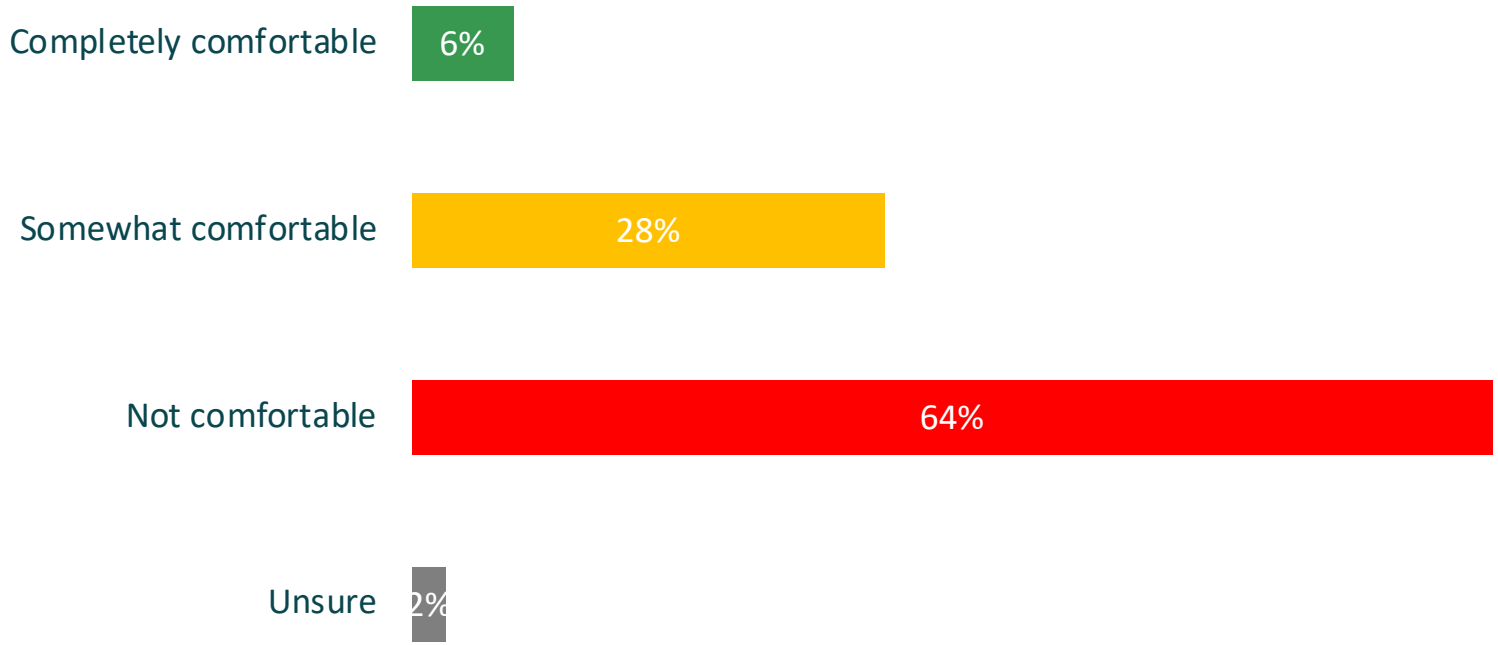
Case Study: British Columbia & Alberta

- British Columbia and Alberta forcibly switched 50,000 patients from their current medicines (physician-prescribed) to the government-chosen biosimilar. **Originator products will no longer be reimbursed. Only certain biosimilars are reimbursed.**
- Canadian Gastroenterology Association and IBD Patient Groups were strongly opposed.



Physician Comfort Level with Third-Party Switching to a Biosimilar

Canadian Survey, Oct. 2017



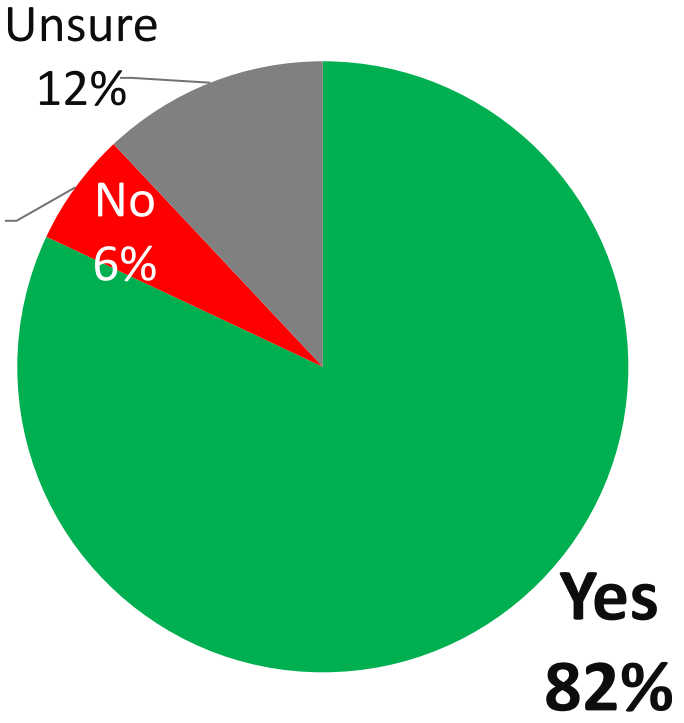
Should Switching Studies Be Conducted Before Automatic Substitution?

Canadian Survey, Oct. 2017

"While provinces have the authority to determine interchangeability and automatic substitution of medicinal products, Health Canada advises against this practice in the case of biosimilars."

Prior to deciding whether automatic substitution should be allowed by a pharmacist or payer,

Do you believe studies should be conducted that measure the effects of switching on patient safety and product efficacy?" (n=403)



These Policies Were Represented to Canadians as Being Similar to European Policies:

"British Columbia (B.C.) is following evidence-based results from a number of international jurisdictions that have over 10 years' experience with these innovative drugs."

"B.C. is leading the country by promoting the widespread use of biosimilars, which have been proven to work just as safely and effectively as higher priced biologics. To date, Canada is far behind European jurisdictions."

-Adrian Dix, Minister of Health,
May 17, 2019

In May 2021, Quebec announced it intends to implement forced-switching.

This despite a report from their own government showing that the safety of switching stable patients was not supported and that Canadian physicians opposed it:

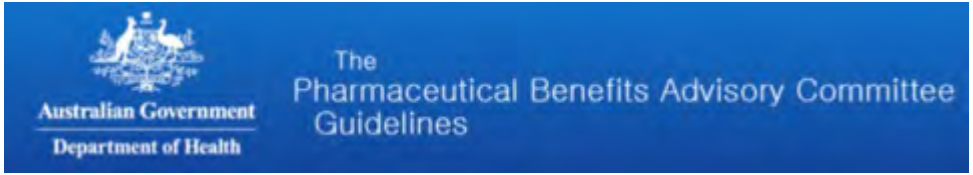
"Non-medical switching in patients being treated with a reference biologic is generally not accepted by learned societies and the consulted clinicians."

– "Safety of switching biologics and their interchangeability", INESS Report (Quebec), May 2020

Non-Medical Switching: Government Payer

Case Study: Australia

- In 2015, Australian Health Minister Sussan Ley announced that Australia would become the **first nation in the world to allow "automatic" substitution of biosimilars.**

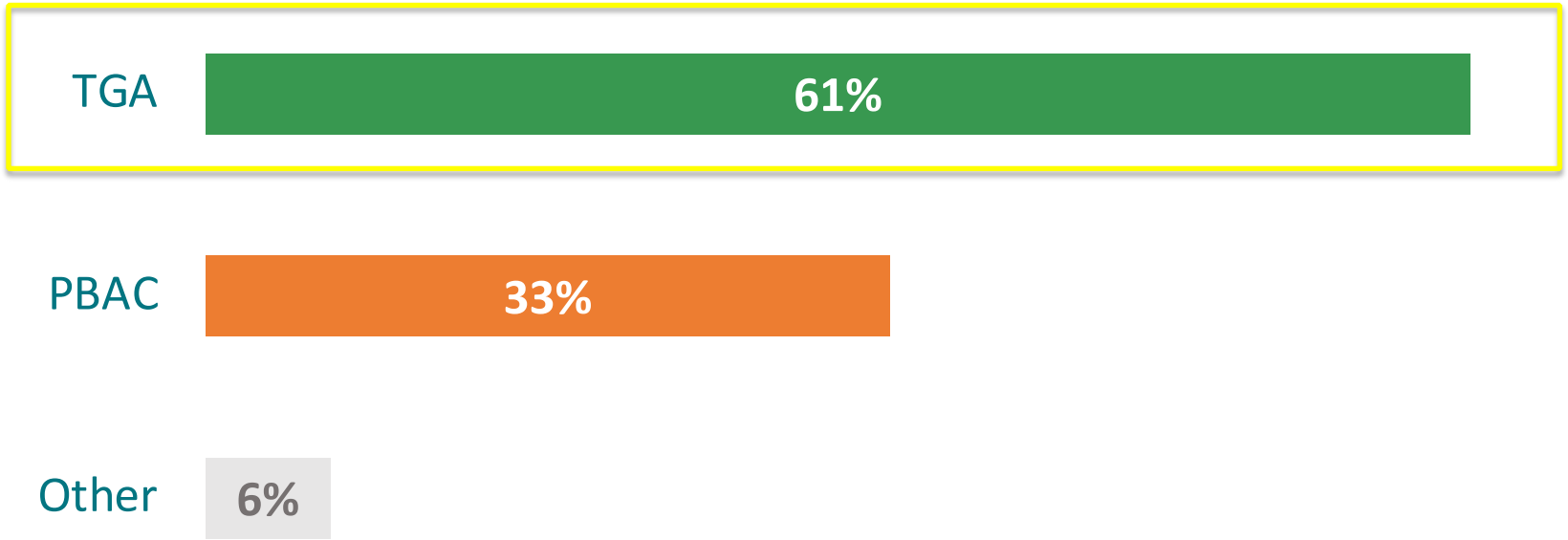


- In Australia this is referred to as "**a-flagging"**
- This move came at the recommendation of Australia's Pharmacy Benefits Advisory Committee (PBAC)- the government payor, not the regulatory agency (Therapeutic Goods Administration).
- **This made substitution an economic non-medical decision rather than a safety decision.**

Australian Survey: Substitution Decision?

Question

"Which body do you believe should be responsible for providing the primary advice to Government that a product is suitable for pharmacy level substitution?"



Physicians Asked for Data

In February 2016, the Australian Rheumatology Association called for **a robust pharmacovigilance program** to be set up for the REMICADE (infliximab) biosimilar INFLECTRA

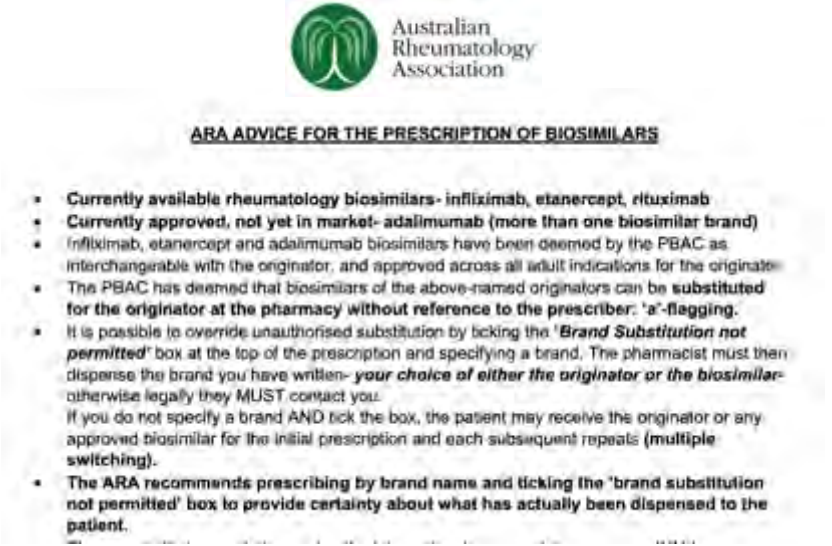
Dr. Mona Marabani (ARA):

- “The ARA wants to see biosimilars successfully introduced to the Australian market, but we have expressed concern with respect to substitution and extrapolation of indications because the evidence is just not there … We are hopeful that collection of data, if done comprehensively, may go some way to establishing an evidence base which is so sorely needed"

Preventing Automatic Substitution

To prevent automatic substitution, physicians have to check a box "brand substitution not permitted" when prescribing. **The Australian PBAC believed that the physicians would not take this extra step.**

Yet, as of July 2020, the ARA still advises its members:



Australian Rheumatology Association

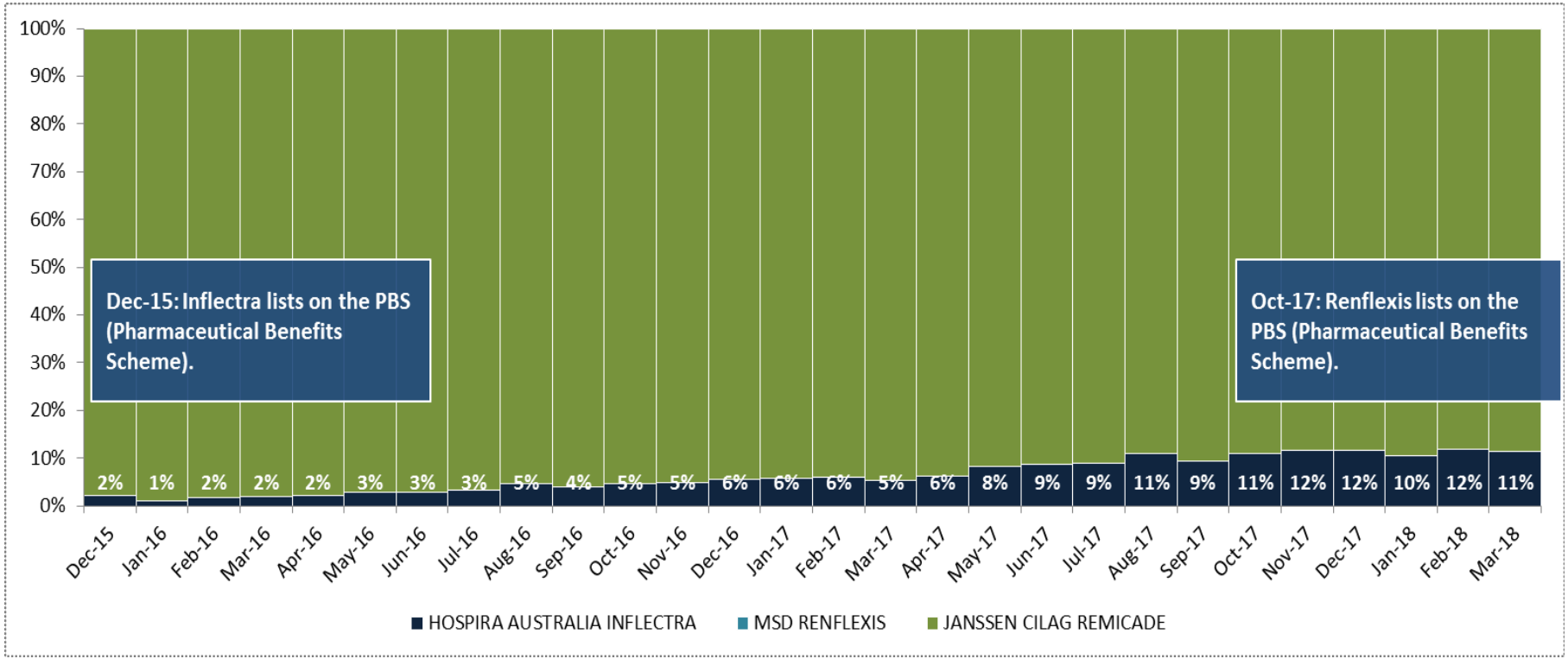
ARA ADVICE FOR THE PRESCRIPTION OF BIOSIMILARS

- **Currently available rheumatology biosimilars- infliximab, etanercept, rituximab**
- **Currently approved, not yet in market- adalimumab (more than one biosimilar brand)**
- Infliximab, etanercept and adalimumab biosimilars have been deemed by the PBAC as interchangeable with the originator, and approved across all adult indications for the originator
- The PBAC has deemed that biosimilars of the above-named originators can be **substituted for the originator at the pharmacy without reference to the prescriber: 'a'-flagging.**
- It is possible to override unauthorised substitution by ticking the '***Brand Substitution not permitted***' box at the top of the prescription and specifying a brand. The pharmacist must then dispense the brand you have written- ***your choice of either the originator or the biosimilar***- otherwise legally they MUST contact you.
  If you do not specify a brand AND tick the box, the patient may receive the originator or any approved biosimilar for the initial prescription and each subsequent repeats **(multiple switching).**
- **The ARA recommends prescribing by brand name and ticking the 'brand substitution not permitted' box to provide certainty about what has actually been dispensed to the patient.**

"If you do not specify a brand AND tick the box, the patient may receive the originator or any approved biosimilar for the initial prescription and each subsequent repeats (multiple switching). **The ARA recommends prescribing by brand name and ticking the 'brand substitution not permitted' box to provide certainty about what has actually been dispensed to the patient."** – *July 2020 ARA Advice for Prescription of Biosimilars*

This practice led to slow biosimilar uptake in Australia as many physicians checked "Brand Substitution Not Permitted"…

Dec 2015 to Mar 2018



Source: IMS Audits data (Australia only); Market Share is measured as share of dosage unit sales (this is to account for compounding).

May 2021: Australia Announces Forced Switching of Stage IV Metastatic Cancer Patients; Patient Advocacy Orgs Push Back.

- Avastin (BEVACIZUMAB) was withdrawn from Australia's Pharmaceutical Benefit Scheme (PBS) as a biosimilar was added.

- Bowel Cancer Australia issued a Patient Alert for Australia's metastatic cancer patients:

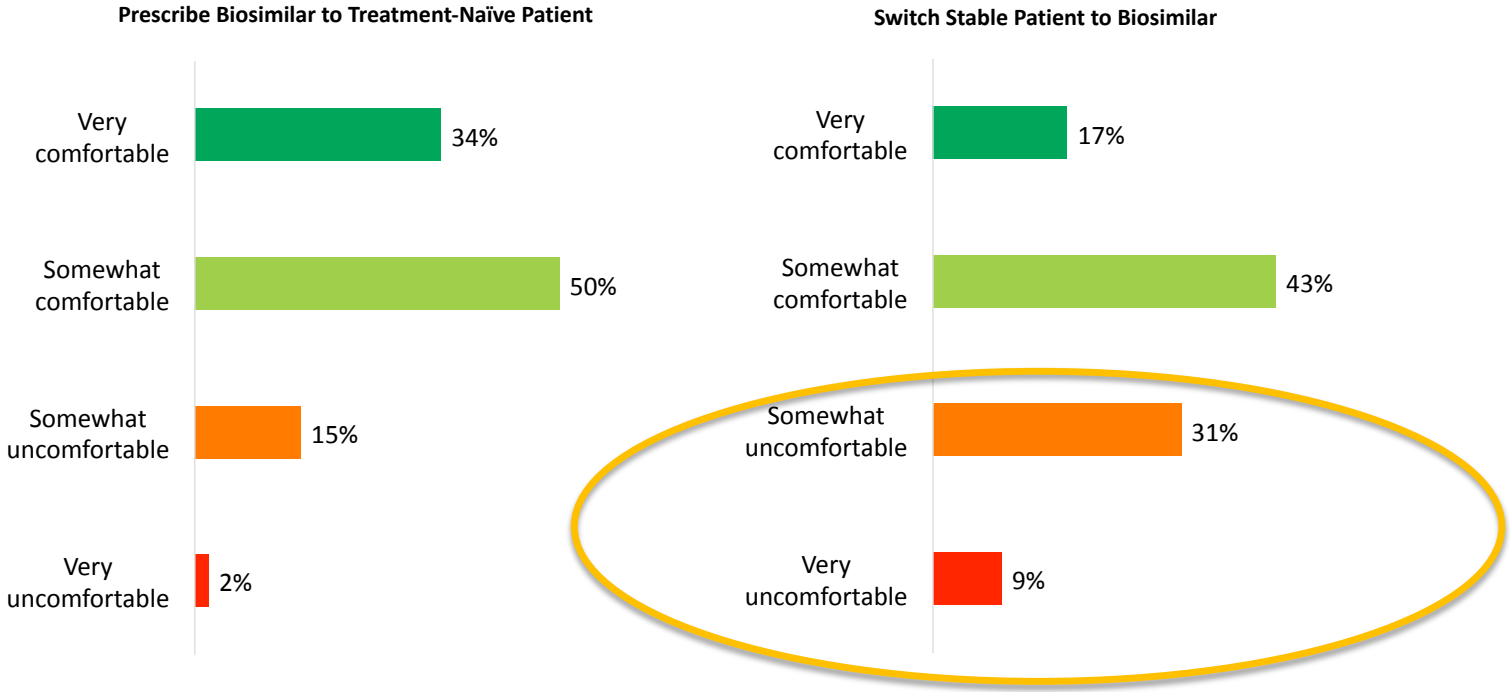
> "The introduction of biosimilars was intended to increase treatment options, but reality suggests the impact will be the opposite…Policies that directly impact patients need to consider patient circumstances and preferences."

Australian patients have organized an e-petition to Parliament, urging reversal of the decision.

Europe: The Leader in Biosimilar Approvals and Commercialization.

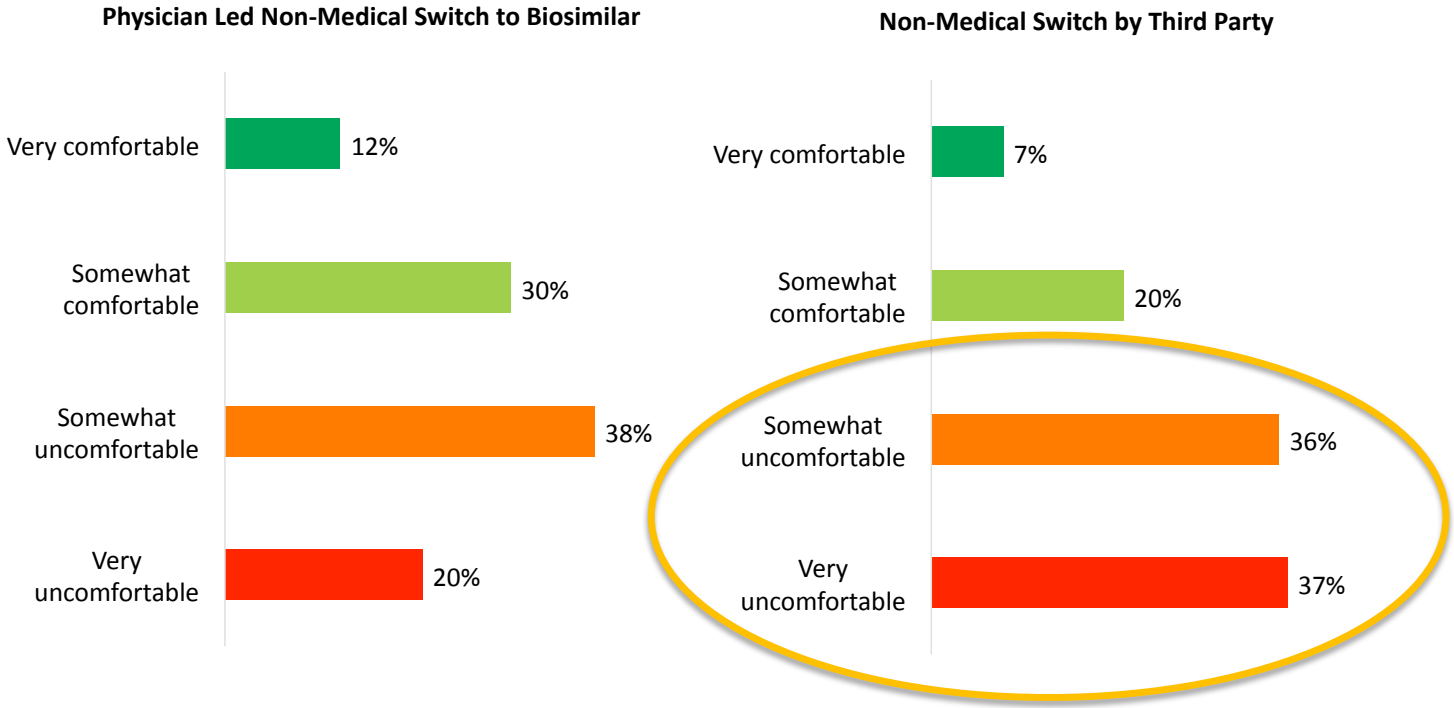
What do its physicians say about biosimilar substitution and non-medical switching?

2019 European Survey: Biosimilars for New vs. Switching Stable Patients



84% are comfortable prescribing biosimilars to treatment-naïve patients. **(40%) are uncomfortable with switching a stable patient to a biosimilar.**

2019 European Survey: Non-Medical and/or Third-Party Switching

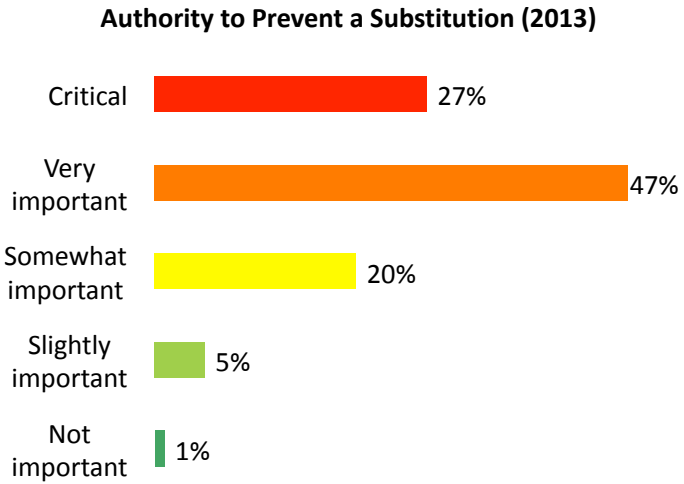


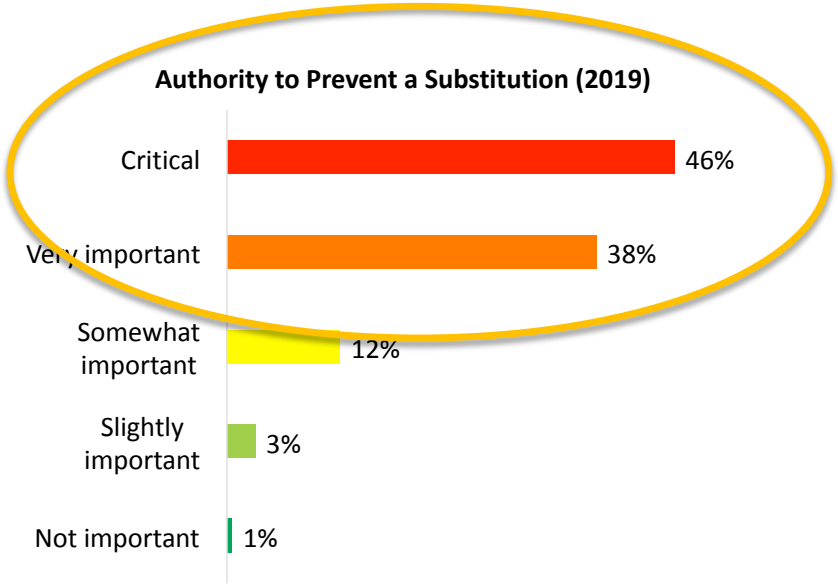
58% are uncomfortable with switching their patients to a biosimilar for non-medical reasons. **This percentage increases to 73% when asked about a third party initiating such a switch.**

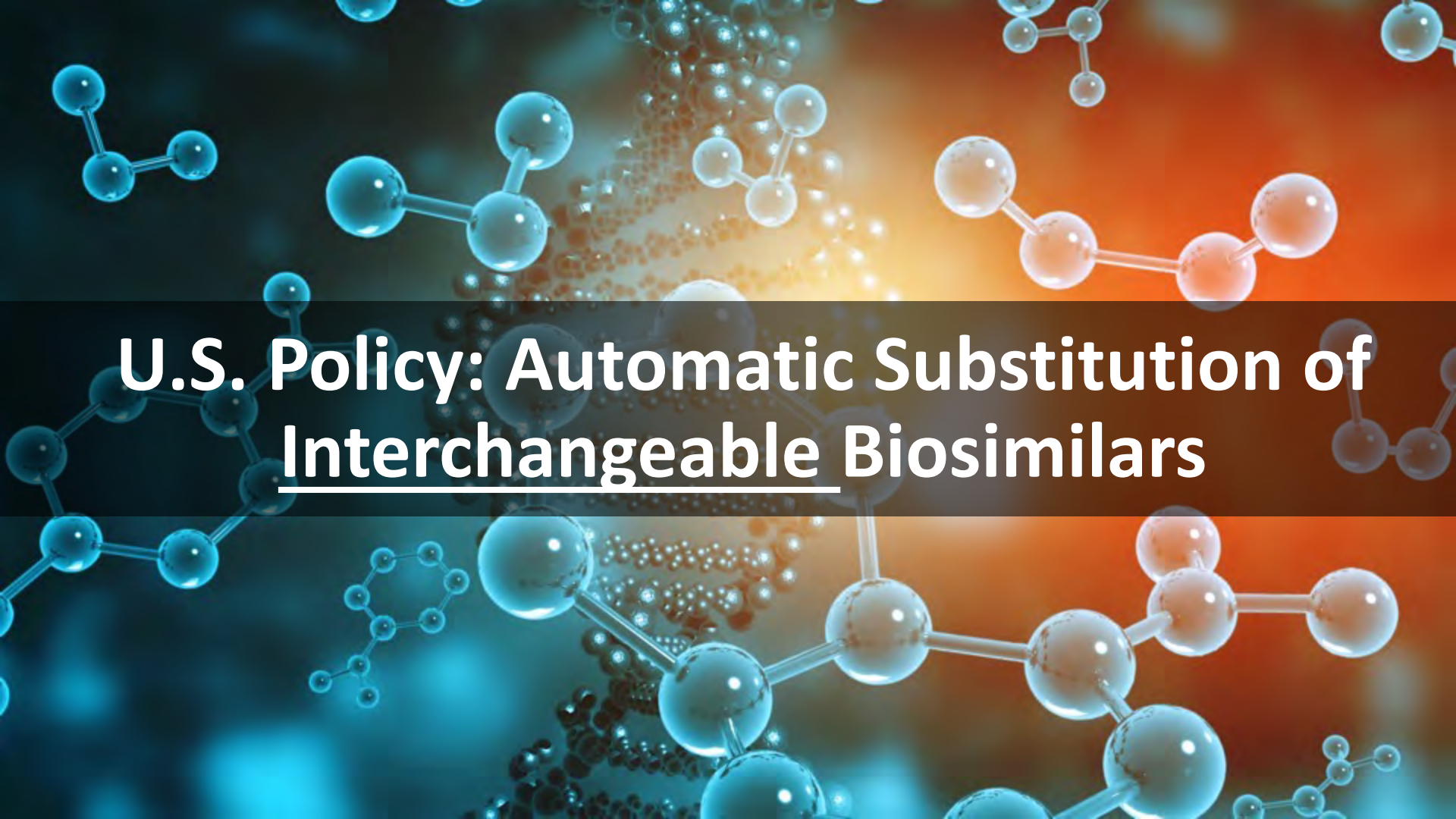
Importance of Authority to Prevent a Substitution Has Increased

Q: "In a situation where substitution by a pharmacist was an option in your country, how important would it be to you to have the authority to designate a biologic medicine as 'DISPENSE AS WRITTEN' or 'DO NOT SUBSTITUTE'?" (n=579)

A strong majority of respondents (84%) consider authority to prevent a substitution either "Very Important" or "Critical", an increase (from 74%) in the 2013 survey.







U.S. Policy: Automatic Substitution of Interchangeable Biosimilars

"Interchangeability" (US-Specific Standard)

US-Specific higher regulatory standard. More data is required, including switching studies.

An "INTERCHANGEABLE" Biosimilar :

1) Must be a **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.**

Objectives of U.S. Substitution Policy

- **Realize the cost savings benefits of biosimilars**.
- **Empower pharmacists** to offer patients lower-cost products.
- Respect the **physician-patient relationship Build physician and public confidence** in biosimilars.
- Use additional FDA data requirements to **address physician concerns** about automatic substitution.
- **Avoid Australia-like situation** where physicians block biosimilars en masse via DAW.

FDA Interchangeability Guidance

Many US physician groups offered comments supportive of the interchangeability guidance.

These included:

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

July 28, 2021

First Interchangeable Biosimilar Insulin Approved by FDA

- **Semglee (insulin glargine-yfgn)** is both biosimilar to, and interchangeable with (can be substituted for), its reference product Lantus (insulin glargine), a long-acting insulin analog.
- Indicated to improve glycemic control in adults and pediatric patients with Type 1 diabetes and in adults with Type 2 diabetes.
- Offered in 10 mL vials and 3 mL prefilled pens, is administered subcutaneously once daily.
- Originally approved in June 2020 under previous 505b(2) pathway and now deemed a biosimilar in the U.S.

Summary

- Physicians have high confidence in biosimilars and are generally very comfortable prescribing them to patients.
- However, many physicians have concerns about switching of stable patients; particularly when initiated by a third party for non-medical reasons (e.g. cost savings, higher profits).
- In the absence of data demonstrating safe switching, physicians and patients have pushed back against forced-switching policies. This has led to reduced biosimilar uptake, particularly where physicians can prevent a substitution.
- Providing additional safety data, and allowing physicians to prevent a substitution they deem medically inappropriate, are tools regulators can use to address physician and patient concerns.

SafeBiologics

ALLIANCE *for* SAFE BIOLOGIC MEDICINES

Thank You For Your Attention