Interchangeability, Switching and Substitution of Biosimilars: Clinical Issues, Challenges

Dr. Freddy J Faccin Lazo
Associate Medical Director – Biotherapeutics
GMA – AbbVie

BIO Latin America Conference
September 9-11, 2014
Rio de Janeiro, Brazil
DISCLOSURE

• Dr. Freddy José Faccin Lazo is a full time AbbVie employee
Interchangeability and Substitution: Working Definitions

• **Interchangeability: Health or Regulatory Authority Designation**
  - US FDA: (1) Expected to produce the same clinical result as the reference product in any given patient; (2) Repeated switching between biosimilar and reference product presents no greater safety or efficacy risk than continued use of the reference product

• **Substitution: Pharmacist Action**
  - When a pharmacist substitutes a certain prescribed product by another equivalent product
  - If without the prescribing physician’s involvement, it is considered “automatic” or “involuntary” substitution

• **Medical Switching: Treating Physician Decision**
  - When a prescribing physician changes medication, usually because of efficacy or safety issue(s)

---

Interchangeability and Substitution

GENERICS

• Regulatory agencies may designate the two as interchangeable
• Depending on local or institutional rules, pharmacists may be authorized or even required to substitute a generic for the original without informing the prescribing physician (automatic substitution)

BIOSIMILARS

• Biosimilarity status by a regulator does not imply interchangeability

Interchangeability/Substitution for Biosimilars: US/FDA

Following passage in 2010 of the Biologics Price Competition and Innovation Act (BPCIA), FDA can deem certain biosimilars as “interchangeable”

Under U.S. law, interchangeable means:

- the biological product is biosimilar to the reference product;
- it can be expected to produce the same clinical result as the reference product in any given patient; and
- for a product administered more than once, the safety and reduced efficacy risks of alternating or switching are not greater than with repeated use of the reference product without alternating or switching.

Substitution is regulated at state level

Interchangeability/Substitution for Biosimilars: EU/EMA

• The EMA’s evaluations **do not include recommendations** on whether a biosimilar could be used interchangeably with its reference medicine:
  – the MA dossier **does not contain evidence** to substantiate an interchangeability determination
  – “For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist.”

• The legal decision on interchangeability is **left to Member States**

• **No country has explicitly authorized interchangeability** for biologicals, including biosimilars

---

Interchangeability and Substitution for Biosimilars

**Canada**
Health Canada does not support automatic substitution, but allows provinces to determine interchangeability.

**US**
FDA requirements to meet interchangeability threshold still unclear, automatic substitution of interchangeable drugs to be determined at state level.

**EMA**
Decision on automatic substitution left to member states - no country has explicitly authorized it. France considers allowing pharmacist substitution for bio-naïve patients.

**Japan**
Interchangeability and automatic substitution highly discouraged.

**Brazil**, **Argentina**, **Mexico**
Developed guidelines for biosimilars, but have not yet addressed interchangeability or automatic substitution.

**Australia**
TGA Guideline states the biosimilar’s PI should include “Replacement of [Reference product name] with [biosimilar product name], or vice versa, should take place only under the supervision of the prescribing medical practitioner.”

---

It was recognized that a number of important issues associated with the use of SBPs need to be defined by the national authorities.

They include but are not limited to the following:

- intellectual property issues;
- interchangeability and substitution of SBP with RBP;
- labelling and prescribing information.

Interchangeability and Substitution: Switching Studies – Design

No one single proposal fulfills requirements for all product classes / disease states

Common needed elements:

- Should be **DB, randomized, controlled trials** (not open labeled)
- Should include **multiple switches (alternation)**
- Should include **appropriate control groups**

Careful consideration should be given to the biotherapeutics’ half-life when defining washout periods

---

Interchangeability and Substitution: Switching Studies – Population

Should switching studies be conducted in the most sensitive populations?

Can clinical interchangeability data themselves be extrapolated from one tested indication to another?

For an indication approved on basis of indication extrapolation can interchangeability be adequately determined?

Interchangeability and Substitution: Switching Studies – Ethical Considerations

• In accordance with the Helsinki declaration, the risk for the individual patient participating in a clinical trial should not overpass the potential benefit\(^1\).

• How to consider a switching study where no clinical benefit is expected while the potential risk might be increased (i.e. an “infinite” risk/benefit ratio)?
  – **Should stable patients on their current treatment be included in switching studies?**

• Can access to affordable medications be considered a sufficient benefit for patients included in switching studies?

• Should switching studies be conducted in patient populations with
  – **Limited therapeutic options**
  – **Critical / life threatening diseases (e.g. oncology)?**

• What will be the alternative treatment for patients who don’t accept the switch (e.g. NOR-SWITCH: continue Remicade™ or switch to Remsima™ to reduce costs – assuming that the drugs are similar)?

---

Interchangeability and Substitution: Additional Considerations

Tracking and Traceability
- Substitution with similar substances may complicate and slow the traceability of an adverse event to a specific drug: long latency periods, non-distinguishable INNs. How will this issue be managed locally and globally?

Post-Market Manufacturing Changes
- Can an interchangeability designation be maintained over time?

Labeling
- Should an interchangeable biosimilar have the same label as the reference product?

Devices
- For self-injectable medications, should new patient be trained after substitution?
- In order to prevent injection errors how similar should the delivery devices be?

Interchangeability and Substitution: Conclusions

- According to the FDA and other reference NRAs, approval of biosimilarity alone is insufficient to establish interchangeability or substitutability with the reference product.

- The challenges facing the design, execution, interpretation and potential clinical consequences of interchangeability studies for biotherapeutics are multiple, and must be addressed from a cross-functional perspective.
  - These challenges must be addressed based on a solid scientific/medical rationale.

- Given the limitations of post authorization data, it is currently impossible to conclude an absence of a risk of switching biologics.

- Until all challenges have been scientifically addressed, only a treating physician in consultation with the patient, should make the decision to switch a patient to an alternative treatment regimen.

Antiepileptic Drugs: New advice on switching between different manufacturer’s products for a particular drug

Advice for healthcare prescribers:

- Different AEDs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control.
- AEDs have been divided into three categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product.
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product, this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder).
- Please report on a Yellow Card any suspected adverse reactions to AEDs ([www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)).
- This advice relates only to AED use for treatment of epilepsy; it does not apply to their use in other indications (eg, mood stabilisation, neuropathic pain).

Additional advice for pharmacists:

- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that AED. Such cases should be discussed and agreed with both the prescriber and patient (or carer).
- Usual dispensing practice can be followed when a specific product is not stated.


Obrigado!
Thanks!
Gracias!

freddy.faccin@abbvie.com