GLOBAL REGULATORY REQUIREMENTS FOR BIOSIMILAR PRODUCTS – ESTABLISHED AND EMERGING REGIONS

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QUESTION #1

Do you think specific scientific and regulatory standards are important for biosimilars?

- Yes, standards are very important as biosimilars are biologic products and should be appropriately regulated
- No, standards should not be stringent for biosimilars
SCIENTIFICALLY APPROPRIATE REGULATORY STANDARDS

- Rigorous scientifically appropriate regulatory standards are necessary for the approval, manufacture, and uninterrupted availability of safe and effective biological products, including biosimilars.
- To create and preserve physician confidence, patient safety, and the integrity of the healthcare system, biosimilars must meet and maintain robust scientific standards before and after approval.
  - Physicians expect that licensed biosimilars have been thoroughly tested and are as safe and effective as the originator product.
- All biological products, including biosimilars, must be held to the same manufacturing quality standards. This will support confidence in biosimilars and help to drive uptake of biosimilars.
GLOBAL BIOSIMILAR REGULATORY STANDARDS

- Most larger markets have developed regulatory guidelines for biosimilars, but some are still lacking consistent and clear pathways for biosimilars.
- The regulatory policies governing biosimilars in emerging markets are still under development, but governments are working to improve and finalize them.
- Many emerging markets have adopted the WHO Similar Biotherapeutic Product guidelines and some follow SRA (e.g., EMA, US FDA) approaches.
- Emerging markets may follow recommendations/approvals (CPP dependence)* from regulated markets (EU, US, Japan Canada and Australia); however, some LATAM countries (e.g., Argentina, Colombia) follow recommendations from other LATAM countries (e.g., Brazil) in addition to the EU and US guidelines.

*The Certificate of Pharmaceutical Product (CPP) is a document issued by a health authority by the request of a product owner to support submission of a medicine to another health authority. The CPP was introduced as a tool to facilitate the regulatory review in the CPP-requesting country.
### A BIOSIMILAR IS NOT...

<table>
<thead>
<tr>
<th>A “Biobetter”¹</th>
<th>Aims to establish <strong>improvements</strong> in safety and/or efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A “Biomimic”, “Biocopy”² or “Noncomparable”³,⁴</td>
<td>So-called &quot;copies&quot; of licensed biologic medicines that <strong>have not been evaluated according to biosimilar standards</strong> and may not have the same level of analytical and clinical similarity as a true biosimilar</td>
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<tr>
<td>A generic drug⁴,⁵</td>
<td>Small-molecule, generally chemically synthesized drugs containing the same active ingredient, strength, dosage form, route of administration, and conditions of use as the reference product and approved under an abbreviated regulatory pathway</td>
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REGULATORY AND DEVELOPMENT REQUIREMENTS FOR BIOSIMILARS DIFFER APPROPRIATELY FROM THOSE FOR THE ORIGINATOR BIOLOGICS

**ORIGINATOR DEVELOPMENT**

Demonstrate safety and effectiveness of a new product with substantial evidence, including one or more adequate and well-controlled clinical trials.

**BIOSIMILAR DEVELOPMENT**

Demonstrate highly similar and no clinically meaningful differences in safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.

**PK = pharmacokinetics; PD = pharmacodynamics.**

CONSIDERATIONS FOR GLOBAL BIOSIMILAR DEVELOPMENT AND APPROVAL

• Most emerging market countries will accept foreign reference product in case the reference biologic is not approved/available and if certain criteria are met
  – Reference product cannot be a biosimilar product – reference product needs to be approved on the full dossier basis
  – Some countries, e.g., China, are not willing to accept foreign reference product for comparability trials against biosimilar
    • May be possible to provide evidence of comparability between product of local origin and foreign product to justify use of data collected using foreign comparator, but foreign comparator product will not be considered the “reference product”

• Some countries, e.g., China, Japan, require local clinical data (i.e., local or ethnic data)

• Approval times can range from 10-months to 36-months, depending on the country and process
EXTRAPOLATION IS A KEY COMPONENT OF BIOSIMILAR DEVELOPMENT

- Extrapolation is the approval of a biosimilar for use in an indication held by the reference biologic not directly studied in a comparative clinical trial with the biosimilar.
- Efficacy and safety from the indication(s) studied using the biosimilar is not extrapolated to other non-studied indications approved for the originator and sought for the biosimilar.
- Overarching principles for extrapolation aligned across global regulatory agencies.
- Extrapolation results in shorter development timeline and potentially faster access to patients.

1. FDA. Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. Published April 2015.
EXTRAPOLATION IS BASED UPON KNOWLEDGE OF THE REFERENCE PRODUCT, TOTALITY OF EVIDENCE, AND SCIENTIFIC JUSTIFICATION\textsuperscript{1}


EXTRAPOLATION

NRAs previous finding of safety and efficacy for the reference product

MECHANISM OF ACTION

PK

IMMUNOGENICITY

EFFICACY AND SAFETY

TOXICITY

SCIENTIFIC JUSTIFICATION

BIOSIMILAR DEVELOPMENT\textsuperscript{2}

Demonstrate biosimilarity to the reference product

Studied Indication

Extrapolated Indication

Extrapolated Indication

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IN ADDITION TO SAFE MANUFACTURING, RELIABILITY OF DRUG SUPPLY IS CRITICAL

Potential Impact of Drug Shortages

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<thead>
<tr>
<th>On Patients</th>
<th>On Healthcare Providers</th>
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<tr>
<td>May need a different therapeutic or course of treatment, which may have different safety and efficacy profiles and cost¹</td>
<td>Drug rationing and need to prioritize patients³</td>
</tr>
<tr>
<td>May be delays in treatment²</td>
<td>Time burden involved in managing shortages⁴</td>
</tr>
<tr>
<td></td>
<td>Errors due to inexperience with alternatives⁵</td>
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Better supply chain performance can:⁶

- **Reduce costs** by shortening manufacturing lead times
- **Improve drug access**, delivering reliable healthcare
- **Improve safety**, reducing human and financial burden of medication errors

QUESTION #2

Pharmacovigilance is important

- For all biological products, including biosimilars
- Only for originator/reference products
PHARMACOVIGILANCE

- To promote pharmacovigilance, all healthcare providers should use a unique product identifier that is carried through all systems that feed into pharmacovigilance
DISTINGUISHABLE PRODUCT IDENTIFIERS

- Distinguishable, unique product identifiers for biological products should be used to facilitate accurate prescribing, dispensing, and pharmacovigilance.
POST-APPROVAL PHARMACOVIGILANCE IS IMPORTANT FOR ALL BIOLOGICS, INCLUDING BIOSIMILARS

- Rigorous pharmacovigilance is essential for all biologics to protect patients and facilitate adverse events to be quickly detected, reported, and attributed to the correct product and manufacturer.

- It is important that all biologics have a unique, distinguishable identifier to accurately identify the product in the medical record.

- No two biological products are identical.

- Biologics are sensitive to manufacturing and handling conditions - problems may emerge for specific products.

- Safety monitoring should have the ability to differentiate between adverse events associated with the biosimilar product vs. those associated with the reference drug or other biosimilars, not simply a product class.

- Pharmacovigilance mechanisms should facilitate targeted regulatory action, when warranted, to ensure patient access.

MULTIPLE APPROACHES TO IMPROVING PHARMACOVIGILANCE FOR BIOLOGICAL PRODUCTS EXIST GLOBALLY – UNIQUE PRODUCT IDENTIFIER IS CONSISTENT

Distinguishable Nonproprietary Naming

FDA will designate a proper name comprised of the “core name” and a distinguishing suffix that is devoid of meaning for all1:

- New originator biologics
- Biosimilars
- Interchangeable biosimilars

Goal: facilitate accurate identification of products by healthcare practitioners and patients, improve pharmacovigilance, and help minimize inadvertent pharmacy substitution of non-interchangeable biosimilar products

Pharmacovigilance Legislation2

Passage of Directive 2010/84/EU and Regulation 1235/2010 aimed at reducing the number of ADRs in the EU through:

- the collection of better data on medicines and their safety;
- rapid and robust assessment of issues related to the safety of medicines;
- effective regulatory action to deliver safe and effective use of medicines;
- empowerment of patients through reporting and participation;
- increased levels of transparency and better communication.

Requirements Include: clear identification of suspected product by name and batch number

Guideline on Good Pharmacovigilance Practices (GVP) entered into force in 2016 and recommended recording of name and batch number

QUESTION #3

Substitution, switching, and interchangeability have the same meaning

• True
• False
DEFINITIONS OF SUBSTITUTION, SWITCHING, AND INTERCHANGEABILITY – TERMINOLOGY MATTERS

- Practice where one drug is dispensed in place of another at the pharmacy level, without consulting the prescribers.\(^1\,2\,\Dagger\)
- Physician may elect to prescribe one medicine in place of another with the same therapeutic intent.\(^2\)
- Physicians should practice evidence-based medicine and consider the risks/benefits of switching patients between an originator product and its biosimilar.
- In Europe, in the context of biosimilars, the term “switching” has been used synonymously with the term “interchangeable.”\(^5\)
- In the US, “interchangeable” is defined by statute to mean that a biosimilar product is expected to behave the same in “any given patient” and that there is no negative impact resulting from alternating or switching between the biosimilar product and the reference product.\(^3\) Most US state pharmacy laws permit automatic substitution at the pharmacy of only biosimilars that FDA has deemed “interchangeable.”\(^4\)

\(^*\)In some US states, there is ongoing dialogue regarding post-dispensing notification and documentation; \(^\Dagger\)private organization management of substitution may vary based on formulary decisions and other factors; \(^\Dagger\)prescribers may indicate “Dispense As Written” and patients may request the originally prescribed biologic medicine.

Slide References
WHAT DOES A DESIGNATION OF “INTERCHANGEABILITY” MEAN IN THE U.S.*

- To be designated an interchangeable biosimilar in the U.S., additional data and information is required to scientifically support the statutory definition and automatic pharmacy-level substitution.

- A designation of interchangeability does not imply anything about the quality of the product
  - Non-interchangeable biosimilars are held to the same quality standards as interchangeable biosimilars

- A designation of interchangeability is not required for physicians to prescribe a biosimilar product in place of the reference product to treatment-naïve patients or patients currently in treatment
  - Physicians should practice evidence-based medicine and consider the risks/benefits of switching patients between an originator product and its biosimilar

FDA = Food and Drug Administration.

*The Biologics Price Competition and Innovation Act (BPCI Act) of 2009 created an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to (and in some cases also interchangeable with) an already FDA-approved biological product. FDA uses this definition of interchangeability when reviewing a request for an interchangeability designation.
THANK YOU FOR YOUR ATTENTION.

QUESTIONS?