Challenges when implementing guidelines for biosimilars

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Agnes V. Klein, MD DPH
Director,
Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics

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Overview

General considerations:

- ❖Regulation of the life-cycle of biological drugs in Canada
- ❖Regulatory context of biosimilars
- ❖What types of challenges has Canada encountered and continues to see in the implementation of biosimilar guidelines?

Challenges and post-market issues of “older biosimilars”

- ❖Are there several “types of biosimilars” ?
- ❖How can regulators have confidence in the quality, safety and efficacy of “older biosimilars”?
- ❖How can the gaps be filled?
- ❖Conclusions

Regulating the life-cycle of biological drugs

- Drugs are “living entities” and have a life-cycle that goes from discovery, through development, use for treatment of disease and, finally, in some instances either removal from market due to safety considerations or due to or lack of use
- Increasingly, it has become clear that this life-cycle must be managed to develop and maintain their benefits and risks at usable levels and in usable form: benefits outweigh risks
- **Life-cycle management of drug products is similar for originators as well as for generics and biosimilars**
- The newest PBRER ICH Guideline (**ICH E2C (R2)** has been adopted by Canada to manage all drugs, including biologicals, following their market authorisation

REGULATORY CONTEXT OF BIOSIMILARS

- In Canada biosimilars are called Subsequent Entry Biologics (SEBs)
- **They are subject to the same regulations and processes as originator biologic drugs**
- A framework guideline provides appropriate interpretation and the context within which biosimilars are regulated
  - The Federal regulator in Canada authorises drugs for market
  - Regulated as drugs under new drug regulations
  - Intellectual property follows data protection provisions similar to the provisions for generics
  - Due to their complex nature there are special considerations for extrapolation of indications
  - There is no declaration of substitutability: this is a provincial matter and an issue related to the practice of medicine

ARE THERE SEVERAL “TYPES OF BIOSIMILARS” ?

- Under Canadian Regulations there is only one type of biosimilar or SEB drug
- In some jurisdictions the “biosimilar” nomenclature applies or applied to a number of biologicals considered essentially identical to the molecule of the originator
- **However, biologicals can never be reproduced as identical molecules and the concept of identity does not apply**
- At minimum, there are unknown risks between various lots and active ingredients considered to be the same
- Therefore, these molecules may be considered only as new biologicals that were marketed without a complete safety, efficacy and quality package. For these the interplay of the three elements were never researched: no data of value exists in respect of these products (literature and theoretical information only)

CHALLENGES IN IMPLEMENTING BIOSIMILAR GUIDELINES

- Manufacturing and pharmaceutical challenges:
  - The source of the API could give rise to impurities that differ from the originator
  - The formulation, while equivalent may have a bearing on the PK/PD properties and, therefore, the dosage of the final product
  - Comparability between the RBP and the biosimilar may not be the same from lot to lot: drifts over time are possible
  - The RBP chosen is not a Canadian product and differs in dosage form, and/or concentration, and/or mode of administration, from those of the biosimilar.
  - There are no bridging rationales in respect of the Canadian product, or a foreign-marketed product; when necessary, studies are missing as sponsors did not consult in advance on requirements

Two biological products meet the standard of being truly similar only at the time of their initial market authorisation

CHALLENGES IN IMPLEMENTING BIOSIMILAR GUIDELINES

- Safety challenges:
  - Is the potential toxicity or safety of the product similar to that of the RBP?
  - The immunogenicity of the two products, the RBP and the biosimilar will likely differ (for ex: EPO)
  - Switching from the RBP to a biosimilar can elicit immune phenomena that were not foreseen
  - We worry mostly about the systemic, generalised immune reactions/secondary diseases
  - Safety-related matters may also have unexpected consequences, clinically

Naming and Traceability for Biosimilars

A biosimilar should have its own brand name (trade name) as for all new medicinal products

International Non-proprietary Name (INN) is within responsibility of WHO. HC currently follows WHO policy, but further discussion is needed on what triggers unique INN

Brand name, INN, DIN, lot/batch number and manufacturer of biological products should be included in adverse reaction reporting

CHALLENGES IN IMPLEMENTING BIOSIMILAR GUIDELINES

- Efficacy challenges:
  - **Difficulties in decision-making when design is not an equivalence trial and margins of equivalence have not been predefined**
  - Outcomes of non-inferiority trials not always as expected:
    - Lead to difficulties around efficacy
    - Acceptable for safety and immunogenicity
  - Considerations around extrapolation of indications
    - Study design not suitable and/or rationale not provided
    - Considerations missing often: pathophysiology of disease/s, patient population enrolled not suitable, PK/PD differences not accounted for, questions of dosage, route of administration, dose ranges, mono or combination therapy
    - Age, sex, race, genomics, not considered
    - Duration of study too short,

CHALLENGES IN IMPLEMENTING OF BIOSIMILAR GUIDELINES

- **There may be other challenges as yet not encountered**, including lack of data
- We are still in our “learning phase” but are taking a pragmatic and operational approach to resolve these until we have learned a sufficient amount to update our guidelines
- We are, however, very careful to be consistent with all decisions
- These decisions must apply to both biosimilars and to new manufacturing methods for originator biologicals

“OLDER BIOSIMILARS”: CONFIDENCE IN THEIR QUALITY, SAFETY AND EFFICACY

- Some countries/regulators have biosimilar products that were never compared to a fully developed originator
- Indications and uses have been “copied” from class indications in “benchmarking” countries
- Very little is known about these products
- Their scientific and medical status is uncertain, but their regulatory status is even more uncertain
- Consequences are gaps on efficacy and more importantly, on risks both real and perceived. The nature of theses risks is unclear and/or unknown

HOW CAN THE GAPS BE BRIDGED?

- Risks can be evaluated and categorized
- The type of categorization will depend on the regulations existing in each country
- Guidelines may be available already. If not, guidelines could be drafted to fit with general scientific and risk-assessment principles that will allow the risk of each product to be evaluated
- Stakeholders should play a role in all of these activities: consultation is important
- Guidelines should contain the minimal requirements for updating of information, especially on the safety side. ICH E2c(R2) can serve as a basis

HOW CAN THE GAPS BE BRIDGED?

- ICH E2C (R2) deals with PBRERs: Periodic benefit-risk assessments for products on the market
- It is important to provide time-lines (sufficient time) for updating information and, if necessary, removal of products from market within each country's regulatory authority
- Overall knowledge of the class of product can be also used to help define risks and time lines
- Use of international information such as warning letters issues by other regulators, etc. can be used to help in these risk evaluations and subsequent course of action
- Standard Operating Procedures and templates for recording information can be very helpful and ensure consistency

HOW CAN THE GAPS BE BRIDGED?

- It is also useful to have annual reports on the quality parameters for each product
- **PBRERs will provide information and an understanding of the ongoing benefits and risks of a product. It is important to keep in mind that perspectives and points of view of all concerned groups may not be the same**
  - **Industry and Partners (development)**
  - **Regulator (independent assessment/decision)**
  - **Patients, Payers, Stakeholders (real-world experience)**
- A learning period is important in all new activities: biosimilars are no exception

HOW CAN THE GAPS BE BRIDGED?

One practical example:

- A biological was seen to have several risks with uncertainties: manufacturing, safety and labelling
- A risk assessment was conducted
- Consultations were undertaken (web-based)
- The risk level was not defined but it became clear that information gaps existed that needed to be bridged
- Sponsors were given up to 2 years to bring the information behind the efficacy, safety and quality of their products up to date
- The process is now ongoing and we are receiving complete submissions

CONCLUSIONS

- Life-cycle management of drug products is similar for originators as well as for biosimilars
- Biosimilars are subject to the same regulations and processes as originator biologic drugs
- Biologics can never be reproduced as identical molecules and the concept of identity does not apply
- Two biologic products meet the standard of being truly similar only at the time of their initial market authorization
- When making changes, appropriate risk assessment, management and communications principles should be considered and followed
- International guidelines are helpful:
  - PBRERs will provide information and an understanding of the ongoing benefits and risks of a product. It is important to keep in mind that perspectives and points of view of all concerned groups may not be the same
- Stakeholders should be consulted for their perspectives
- Timelines for implementation are very desirable

Thank You

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