Updates on biosimilars

Member State Meeting

1 December 2022

WHO Access to Medicines and Health Products Division

World Health Organization

Outline

- Mandate WHA67.21
- Opportunities and challenges
- Regulatory issues
    - Standardization and regulatory convergence
    - PQ
    - Nomenclature
- Access issues
    - Selection and use
    - Affordability
- Going forward

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WHA67.21 “Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy”

- Recognized that biotherapeutic products could be more affordable and offer better access to treatments of medicines from biological origin, while ensuring their quality, safety and efficacy and
- Requested the DG to:
  - support Member States in strengthening their capacity in regulation;
  - to support, the development of national regulatory frameworks;
  - to encourage and promote cooperation and exchange of information;
  - and to convene the WHO Expert Committee on Biological Standardization to update the 2009 guidelines on the evaluation of similar biotherapeutic products

Biotherapeutic products *are biologicals with the indications of treating human diseases which are grown and then purified from large-scale cell cultures of bacteria or yeast, or plant or animal cells.*

A ***biosimilar biotherapeutic product*** *is a biological product that is shown to be similar in terms of quality, safety and efficacy to an already licensed reference biological product.*

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Introduction

Opportunities

- Many countries have regulatory frameworks in place
- A range of biosimilars in key therapeutic areas such as cancer, diabetes and rheumatoid arthritis are available
- Better affordability as compared to innovator products
- More therapeutic options

Challenges

- Regulatory: Lack of regulatory expertise and capacity, insufficient resources in countries and lack of availability of reference standards.
- Policy: Lack of inclusion in reimbursement and financing schemes, clinical treatment guidelines, guidance on interchangeability or possibility of substitution.
- Market factors: Dominance by larger manufacturers, small markets for some products, lack of price transparency, intellectual property and trade barriers
- Demand: Lack of knowledge, acceptance of or uncertainties around biosimilars amongst prescribers and patients.

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Guidelines on evaluation of biosimilars

May 2014

WHA 67.21

Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy

Aug 2014

16th International Conference of Drug Regulatory Authorities (ICDRA): 5 recommendations to WHO as actions to be taken to implement the resolution

1. Ensure regulatory oversight throughout the life cycle
2. Improve efficiency of regulatory evaluation
3. Amend and facilitate implementation of WHO GLs
4. Collaboration with regulators & relevant stakeholders
5. Regulatory convergence as a tool to increase global access

2014-2020

Established guidance documents for life cycle management and international reference standards for consistency and traceability throughout life cycle

Consultation and publication on collaborative assessment and recognition of the decision by other NRAs on the evaluation of post approval changes

Organized 6 implementation workshops & developed 11 case studies

Collaboration with International Pharmaceutical Regulators Programme (IPRP), e.g. template & examples of Public Assessment Summary Information, e-learning materials

Surveys conducted as a tool to measure progress in regulatory convergence (2019-2020)

2021

Conducted a review on current scientific evidence and experience

Published a review article titled “Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience”

Review includes the relevant GLs from other jurisdictions, a literature search on S & E information, a search on the role of clinical studies.

Recommendations for revision provided.

April 2022

Revised Guidelines on evaluation of biosimilars (adopted by the Expert Committee on Biological Standardization (ECBS))

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Surveys in 2019 & 2020

Regulatory landscape changes and progress made in regulatory convergence (2019)

- Significant progress in adoption of WHO GLs on regulatory evaluation of biosimilars.
- Many countries have regulatory frameworks for biosimilar approval in place. This has prompted the increased rate of approval of biosimilars worldwide.
- A range of biosimilars is now available particularly in key therapeutic areas such as cancer, diabetes and rheumatoid arthritis.
- Progress made in converging on consensus use of the term “biosimilar”.

Challenges and areas where further support needs to be provided to MS (2020)

- Accepting foreign licensed and sourced reference products (Note: addressed in the revised GLs).
- A lack of regulatory expertise and insufficient resources in countries which requires a lengthy process of capacity building.
- A significant problem with the quality of copy-version products approved without demonstration of biosimilarity.
- No consensus among countries on the practice of interchangeability and naming of biosimilars.

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Key updates in revised GLs, April 2022

Focus on scientifically necessary data to save cost and time in animal and human trials and to speed up the availability of biosimilars

- Scope, expanded: “biotherapeutics” to “biologicals”.
- Terminology: corresponding shift to “biosimilar” rather than “similar biotherapeutic product”.
- Clarification in the use of foreign licensed and sourced reference products, i.e. non-local products
  - Accepting these reference products contributes to expanding the availability of various product classes, since the originators might not be available on the markets of certain countries prior to approval of the biosimilars.
- Use of international standards and reference reagents contributing to life-cycle management, i.e. consistency, traceability.

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- No obligation on animal studies
  - implementation of the 3Rs principles (“Replace, Reduce, Refine”) to minimize the use of animals in testing.
  - “…in vivo animal studies would be expected to represent a rare scenario.”
- Flexibility provided on the amount and type of clinical data required, i.e. considering case by case need
  - “…comparative efficacy and safety trial will not be necessary if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise.”
- The role and responsibilities of NRAs highlighted, e.g.
  - Improve the efficiency of regulatory evaluation and avoid the unnecessary duplication of studies

Next steps

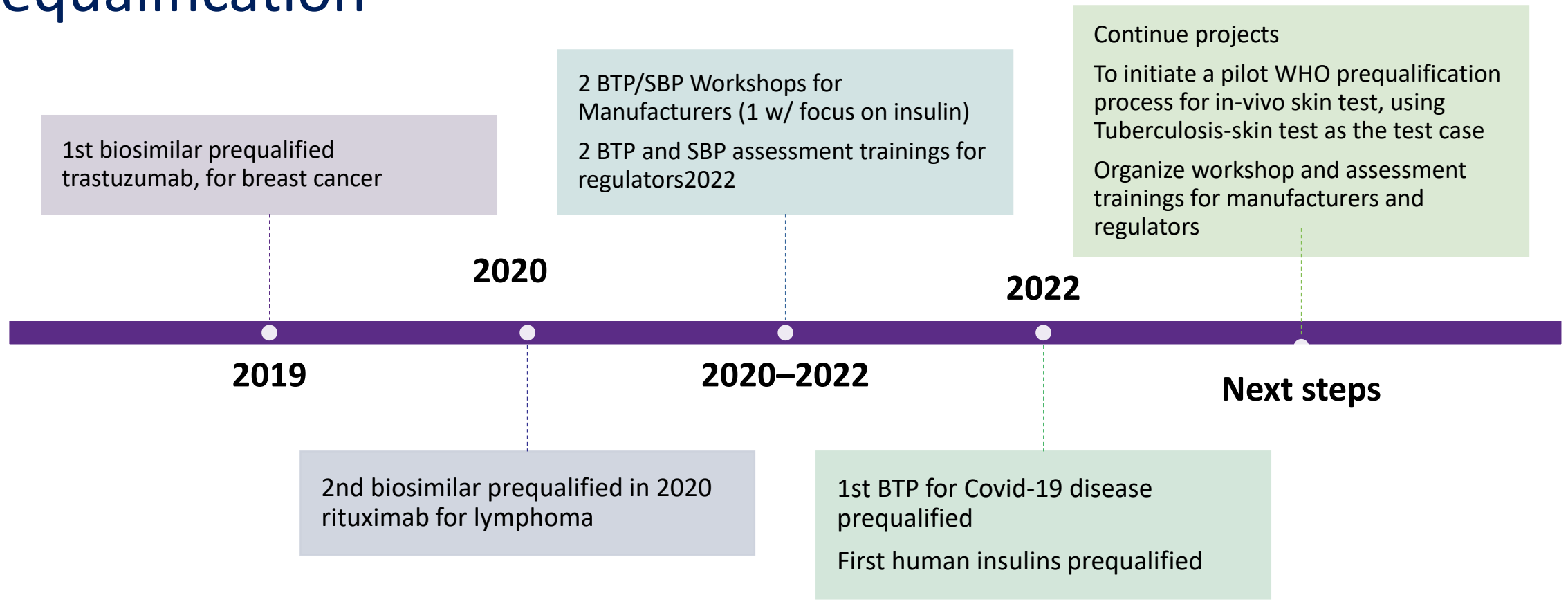
Implementation of principles outlined in the revised GLs

- Develop case studies for illustrating the regulatory review of application
- Organize workshops to practice case studies
- Publish training materials available for all regulators
- Collaborate with regulators and other relevant stakeholders to develop e-learning materials and to organize seminars/courses

Building trust in biosimilars

- Develop tools to communicate with and educate all stakeholders
- Make effort to distinct copy-version (non-innovator) products other than biosimilars to increase public trust in biosimilars and confidence in their use
- Encourage NRAs to review and assess the copy-version products existed on the markets prior to the establishment of regulatory framework for biosimilars

Prequalification



Facilitates procurement of safe, efficacious and quality assured products by UN agencies and national authorities with limited resources

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Nomenclature

Challenges

- Biological substances comprise more than 50% of applications to the INN Programme and the percentage is increasing.
- Nomenclature needed to distinguish different forms of same biotherapeutics.
- Need to avoid proliferation of separate and distinct national qualifier systems.
- Need to improve traceability and pharmacovigilance to increase trust, uptake and reduce price

Progress and next steps

- Biological qualifier scheme proposed
- Consultations held with stakeholders
- Concept note for WHO Management
- Requirements
  - A database managed by WHO
  - Additional staff resources
  - Self- funded: small fee levied for each application
  - Scheme managed by WHO in collaboration with NDRAs.

BQ will assist in the identification of biological substances for:

- prescription and dispensing
- Pharmacovigilance
- transfer of prescription globally

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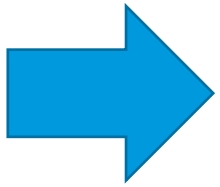
Evidence based selection

Progress

- Biosimilars now explicitely listed on the WHO Model List of Essential Medicines (EML) for:
  - Anti-TNF, Asparaginase, Pegaspargase, Rituximab, Trastuzumab, Filgrastim, Nivolumab/pembrolizumab, Erythropoietins, Low-molecular-weight heparin (LMWH), Insulin (including long-acting analogues), Anti rabies virus MAB, Bevacizumab (eye)
- Interchangeability explicitly recommended for Anti-TNF, Erythropoietins, LMWE and Insulins

Next steps

- Expand listing to other biosimilars



- Facilitates selection for procurement and reimbursement of biosimilars by national authorities
- Expands availability of more affordable products

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WHO Guideline on country pharmaceutical pricing policies

10 policies

External reference pricing

Internal reference pricing

Value-based pricing

Mark-up regulation

Promoting price transparency

Tendering and negotiation

Promoting the use of quality-assured generic and biosimilar medicines

Pooled procurement

Cost-plus pricing

Tax exemptions or tax reductions

Strong recommendations for generic and biosimilars

Enable early market entry of generic and biosimilar medicines through legislative and administrative measures with a view to encouraging early submission of regulatory applications, allowing for prompt and effective review, and ensuring these products are safe, efficacious and quality-assured.

Use multiple **pricing policies to achieve low prices for generic and biosimilar medicines** that are informed by the cost of production eg.: internal reference pricing, mark-up regulation, direct price controls, tendering, promoting price transparency and lower patient co-payments.

Implement, and enforce as appropriate, a suite of policies [… e.g. generic and **biosimilar substitutions, prescribing by INN and financial and non-financial incentives**]

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Going forward

- Support implementation of the guidelines on evaluation of biosimilars (case studies, workshops, training)
- Build trust in biosimilars at the national level (develop tools to educate stakeholders including prescribers and patients)
- Continue PQ projects and training for manufacturers and regulators
- Continue consultation on BQ scheme
- Expand biosimilars on EML
- Harmonize clinical guidelines and national essential medicines lists
- Develop and support policies to promote the use biosimilars (e.g.pricing policies)

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Thank you

www.who.int/teams/health-product-policy-and-standards/overview

https://www.who.int/teams/regulation-prequalification/overview

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