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IPRP Biosimilars Working Group Workshop: “Increasing the Efficiency of Biosimilar Development Programs-Re-evaluating the Need for Comparative Clinical Efficacy Studies (CES)”

IPRP Biosimilars Working Group (BWG)

Session 1: Setting the stage—How have we been using comparative clinical efficacy studies (CES) in biosimilar development programs, and what have we learned?

Tuesday, 12 September 2023

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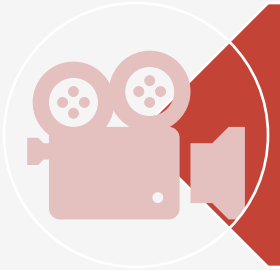
Welcome

Chat, microphone, and video are disabled for attendees

Please use the Q&A function to input any questions you would like addressed by our panelists



The session is being recorded

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Overview of Session

- Opening Remarks (10 mins)
  - Carol Kim, US FDA
- Regulatory Experience and Considerations to Date (110 min)
  - Marie-Christine Bielsky, MHRA
  - Hye-Na Kang, WHO
  - René Anour, EMA
  - Bradley Scott, Health Canada
  - Ryosuke Kuribayashi, PMDA
  - Woo Yong Oh, MFDS
  - Stacey Ricci, US FDA
- Q&A with Speakers and other Regulator Representatives (50 mins)
  - Moderator: Ali Al Homaidan, SFDA
- Closing Remarks (10 mins)
  - Carol Kim, US FDA

IPRP Biosimilar Working Group Background

Chair: Sarah Yim, US FDA Co- Chair: Ali Al Homaidan, SFDA

Scope

- To discuss regulatory challenges and potential topics/areas for harmonization or convergence regarding biosimilars
- To consider how regulatory convergence can be achieved and how regulatory information can be exchanged without compromising confidentiality
- To explore work sharing process with other international bodies and to collaborate in terms of training of international regulators

Objectives

- Regulatory convergence: For regulatory convergence of technical requirements for biosimilar products in facilitating the regulatory process
- Regulatory frameworks: To support international regulators develop safe and effective regulatory frameworks for biosimilar products

Participants

- ANVISA, Brazil
- COFEPRIS, Mexico
- CPED, Israel
- EAC
- EC, Europe
- EDA, Egypt
- FDA, United States
- GHC
- Health Canada, Canada
- HSA, Singapore
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- MHRA, UK
- NRA, Iran
- PAHO/PANDRH
- SAHPRA, South Africa
- SFDA, Saudi Arabia
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- TGA, Australia
- TITCK, Turkey
- WHO

https://www.iprp.global/working-group/biosimilars

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US FDA Effort to Streamline Biosimilar Development

September 20-21, 2021 Workshop

- **"Pharmacodynamic Biomarkers for Biosimilar Development and Approval"**
- Discussion on the current and future role of pharmacodynamic (PD) biomarkers in improving the efficiency of biosimilar product development and approval
- Focused on leveraging PD biomarkers for biosimilar development and approval

September 19, 2022 Workshop

- **"Increasing the Efficiency of Biosimilar Development Programs"**
- Discussion on comparative clinical studies associated with biosimilar development programs
- Focused on innovative ideas including statistical methods to streamline and improve the efficiency of biosimilar development

Purpose of the Workshop

- Goal: Increase efficiency in Biosimilar development programs
- How: Re-evaluate the need for comparative clinical efficacy studies in biosimilar development programs based on the experience accrued from international regulatory experts and external subject matter experts
- Public Sessions:
  - Day 1: Regulator perspectives on how have we been using comparative clinical efficacy studies in biosimilar development programs and what have we learned
  - Day 2: Stakeholder perspectives on the pros and cons of comparative efficacy studies in biosimilar development programs
- Regulators Sessions:
  - Discuss regulatory considerations for streamlining biosimilar development programs
  - Discuss considerations around when comparative efficacy studies may or may not be needed

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Moderator

Ali Al Homaidan, PhD, FDA, Kingdom of Saudi Arabia

Ali Alhomaidan is a highly accomplished executive with a track record in the Pharmaceutical and Biotech sectors. Currently serving as the Vice-chair of the IPRP Biosimilars working group, Ali has devoted over two decades to the Saudi FDA, where he has held various pivotal roles. Notably, he served as the Executive Director of Products Evaluation and Standards Setting, as well as the Director of Biological Products Scientific Evaluation. Ali's academic credentials include a Doctorate in Biotechnology from the University of Queensland, Australia, and a Certificate of Management Excellence from Harvard Business School, USA. His extensive experience, combined with his academic achievements, underscores his commitment to advancing the pharmaceutical and biotech industries.

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Speaker #1

Marie-Christine Bielsky, MD, MHRA, United Kingdom

After studying medicine in Strasburg (France), she made a career in the pharmaceutical industry, where she participated in the clinical development of a wide range of medicines, including orphan and biological drugs. In 2006, she joined as a medical assessor the Biologicals and Biotechnology Unit of the Licensing Division at the UK Regulatory Agency. She was a member of the Biosimilar Medicinal Products Working Party at the European Medicines Agency, where she participated in the drafting of several biosimilar guidelines and in the assessment of several biosimilar products (insulins, G-CSFs, infliximab, rituximab, bevacizumab, adalimumab). She was part of the drafting group of the Guidance on the licensing of biosimilar products issued by the MHRA in 2021.

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Speaker #2

Hye-Na Kang, V.M.D., WHO

- Dr. HyeNa Kang is a Scientist in the Norms and Standards for Biological Products (NSB) team of the World Health Organization (WHO), Switzerland.
- Dr Kang joined WHO HQ in January 2009 and has been in charge of development/ implementation of WHO guidelines for regulatory evaluation of biologicals, particularly biotherapeutics including biosimilars. She has coordinated the works to provide regulatory principles in biotherapeutic area and organized many workshops. She has also coordinated works to develop case studies and published many articles to implement the evaluation principles of WHO guidelines into regulatory practices in countries. She is a member of Biosimilar Working Group of the International Pharmaceutical Regulators Programme.
- Prior to joining WHO, Dr Kang was a scientific officer for twelve years at Korea Ministry of Food and Drug Safety (formerly Korean Food and Drug Administration) who was responsible for reviewing license applications, quality control test, and facility inspection of bacterial vaccines, blood products, plasma-derived products, and tissue transplant products. In 2004, she worked on the project to develop HCV DNA vaccines at the Vaccine and Infectious Disease Organization-International Vaccine Center in the University of Saskatchewan in Canada.

WHO Activities related to regulatory standardization of biosimilars

Dr Hye-Na KANG

Norms and Standards for Biological products (NSB Team), WHO HQ

- IPRP BWG workshop, Virtual, 12 Sept 2023

World Health Organization

75 HEALTH FOR ALL

Outline:

1. **Implementation of the Resolution of 2014 WHA**
2. **Outcomes of review and survey conducted in 2019 & 2020**
3. **Key update in the revised GLs, 2022**

Disclaimer: The speaker is a staff member of the World Health Organization. The speaker alone is responsible for the views expressed in this presentation and they do not necessarily represent the decisions, policy or views of the World Health Organization.

WHA Resolution & Implementation

- WHO *Guidelines on evaluation of similar biotherapeutic products (SBPs)*, adopted by the ECBS* in 2009 (Annex 2, WHO Technical Report Series No. 977).
- WHA* 67.21 Resolution in 2014, "Access to biotherapeutic products (BTPs) including biosimilars and ensuring their quality, safety and efficacy": To convince ECBS to update the 2009 guidelines:
  1. taking into account the technological advances for the characterization of BTPs; and
  2. considering national regulatory needs and capacities.

Resolution to update the 2009 GLs	1. taking into account the technological advances for the characterization of BTPs	2. considering national regulatory needs and capacities
Activities & Report to ECBS	• Current scientific evidence and experience gained reviewed in 2020 • Informal consultation held in 2021	Survey conducted in 2019 & 2020
Publications	1 article & meeting report	3 articles

**ECBS: WHO Expert Committee on Biological Standardization*

**WHA: World Health Assembly*

Review of scientific evidence and regulatory experience in 2020

Aim of review

- To review scientific evidence and experience to identify issues/cases for further reducing nonclinical and clinical data
- To reach consensus on regulatory considerations and expectations for evaluation of biosimilars
- To update the GLs with providing more flexibility

Methodology

- Review the relevant GLs, e.g. US FDA, EMA, HC
- Review the literature for long-term experience with biosimilars, e.g. EPAR, journal publications for long-term efficacy and safety of biosimilars for the years 2017 – 2020, systematic reviews published in 2017-2020 to cover older data.
- Evaluate the roles and relevance of clinical efficacy studies for the benefit-risk assessment of biosimilars for the possibilities to reduce clinical data requirements

Key finding

- WHO 2009 GLs to be updated to reflect the current scientific knowledge.
- Long-term safety, efficacy and immunogenicity data of licensed biosimilars since 2006 do not raise concerns.
- Current data could suggest that state-of-the-art analytical and functional testing and robust PK and PD studies are sufficient to demonstrate biosimilarity, whereas in vivo animal studies and large confirmatory efficacy and safety studies are generally not needed.

NOTE

- *The review and analysis are based on the view of authors and they do not necessarily the views of WHO.*

Survey conducted in 2019 & 2020

Aim of survey

- To describe the progress made and the regulatory landscape change for biosimilars in 21 countries during the past 10 years.
  - WHO Guidelines on evaluation of biosimilars issued in 2009
  - A survey to review the regulatory situation in countries conducted in 2010 (Biologicals 39, 2011)
- To identify challenges and areas where further support to Member States needs to be provided.

Countries

- Regulatory experts from 20 countries covered all WHO 6 regions: AF (Ghana, Zambia), AM (Brazil, Canada, Cuba, Peru), EM (Egypt, Iran, Jordan), EU (Russia, Ukraine, UK), SEA (India, Indonesia, Thailand), WP (China, Japan, Malaysia, Korea, Singapore) + USA

Focuses

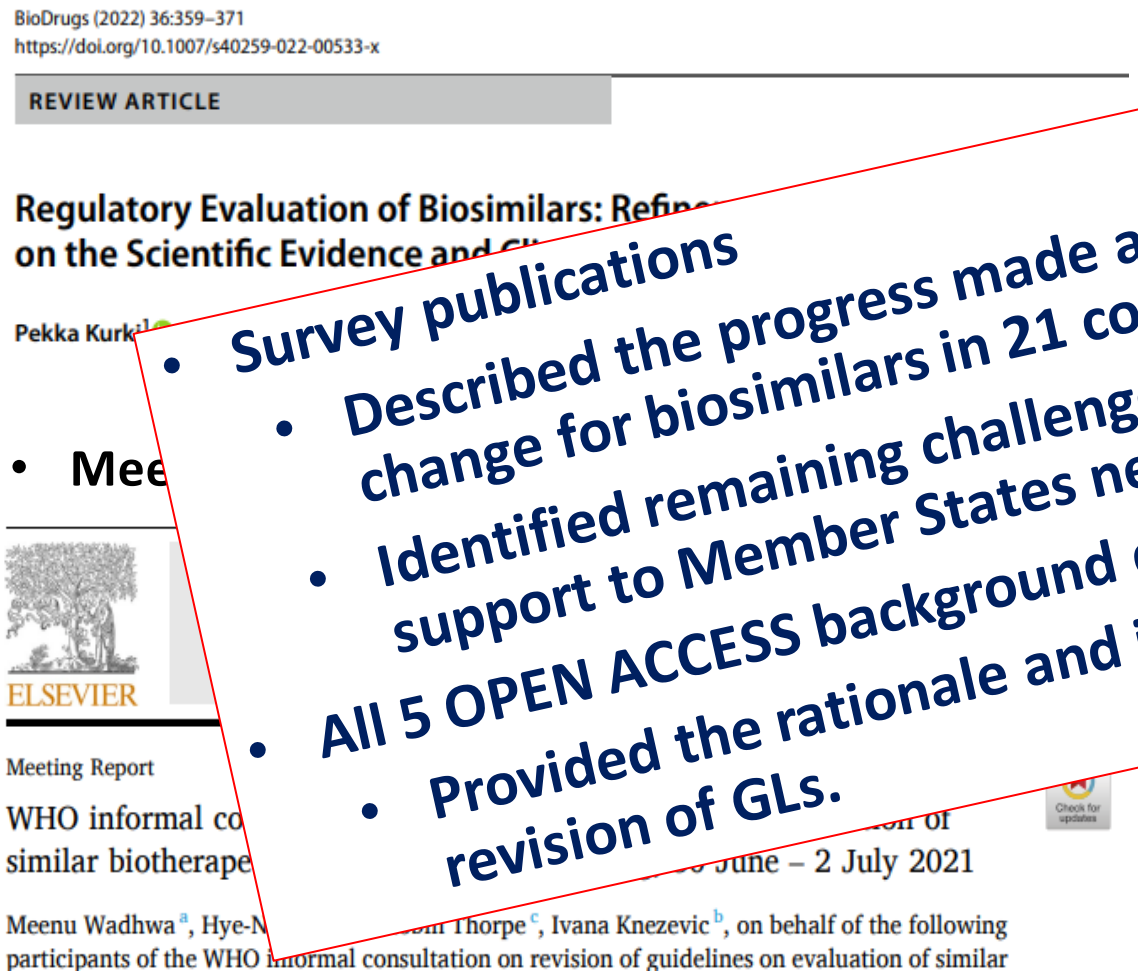
Aug 2019: Situations	June 2020: Challenges
Regulation/Guidelines	Reference products
Terminologies	Resources
Approval of biosimilars	Quality of biosimilars
Biosimilars under development	Issues related to the use

NOTE

- *Assessment based on the data submitted by survey participants from 20 countries. Thus, biosimilars approved in certain countries might not have been approved following a strict regulatory process as recommended by WHO 2009 GLs.*

Publications

- **Review published, *BioDrugs* 36, 2022**


BioDrugs (2022) 36:359–371
https://doi.org/10.1007/s40259-022-00533-x

REVIEW ARTICLE

Regulatory Evaluation of Biosimilars: Refin
on the Scientific Evidence and Cl

Pekka Kurki[1]

- Mee

ELSEVIER

Meeting Report

WHO informal co
similar biotherape
June – 2 July 2021

Meenu Wadhwa[a], Hye-N
Thorpe[c], Ivana Knezevic[b], on behalf of the following participants of the WHO informal consultation on revision of guidelines on evaluation of similar

- **Survey outcomes published: *Biologicals* (2020), *Ann NY Acad Sci* 15
Bi journal (2020)**


ScienceDirect

n/locate/biologicals

ts and progress made

ts from 19 countries

nn. N.Y. Acad. Sci. ISSN 0077-8923

similars: an update

Thorpe,[2] Ivana Knezevic,[1] Mary Casas Levano,[3]
ice Chilufya,[4] Parichard Chirachanakul,[5] Hui Ming Chua,[6] Dina Dalili,[7]
eddie Foo,[8] Kai Gao,[9] Suna Habahbeh,[10] Hugo Hamel,[11] Gi Hyun Kim,[12] Violeta Perez
Rodriguez,[13] Desi Eka Putri,[14] Jacqueline Rodgers,[15] Maria Savkina,[16] Oleh Semeniuk,[17]
Shraddha Srivastava,[18] João Tavares Neto,[19] Meenu Wadhwa,[20] and Teruhide Yamaguchi[21]

GaBiJournal
Generics and Biosimilars Initiative Journal

ORIGINAL RESEARCH

Biosimilars for Healthcare Professionals

Biosimilars – status in July 2020 in 16 countries

Hye-Na Kang[1], PhD; Robin Thorpe[2], PhD; Ivana Knezevic[1], PhD; Daehyun Baek[3], PhD; Parichard Chirachanakul[4]; Hui Ming Chua[5]; Dina Dalili[6], PhD; Freddie Foo[7], MSc; Kai Gao[8], PhD; Suna Habahbeh[9], PhD; Hugo Hamel[10], PhD; Edwin Nkansah[11], PhD; Maria Savkina[12], PhD; Oleh Semeniuk[13]; Shraddha Srivastava[14]; João Tavares Neto[15], PhD; Meenu Wadhwa[16], PhD; Teruhide Yamaguchi[17], PhD

- **Survey publications**
  - **Described the progress made and the regulatory landscape change for biosimilars in 21 countries during the past 10 years.**
  - **Identified remaining challenges and areas where further support to Member States needs to be provided.**
- **All 5 OPEN ACCESS background documents**
  - **Provided the rationale and improved transparency for the revision of GLs.**

Key updates incorporated in the revised GLs, 2022

	2009	2022	Reasons for updates
Terminology and Definition	Similar biotherapeutic product (SBP): Biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP).	Biosimilar: Biological product that is highly similar in terms of its quality, safety and efficacy to an already licensed reference product (RP).	In order to align with an internationally recognised harmonised terminology and to expand to include the evaluation of biological products other than biotherapeutics alone, e.g. palivizumab used prophylactically.

Key updates incorporated in the revised GLs

	2009	2022	Reasons for updates
Scope of guidelines	Apply to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines and plasma-derived products and their recombinant analogues are excluded from the scope of this document.	Apply to biological products that can be well-characterized, such as recombinant DNA-derived therapeutic peptides and proteins. Some of the principles provided in these Guidelines may also apply to low-molecular weight heparins and recombinant analogues of plasma-derived products. Vaccines and plasma-derived products are excluded from the scope of these Guidelines.	The scope expanded and clarified. In addition, the term 'well-established' deleted to avoid confusing with the term 'well-established use' in EU and its meaning added in the definition of RP, i.e. 'marketed for a suitable period of time with proven quality, safety and efficacy'. *NOTE: Vaccines (e.g. mRNA) are excluded but may be considered in the future.*

Key updates incorporated in the revised GLs

	2009	2022	Reasons for updates
Key principles for licensing	The development of an SBP involves stepwise comparability exercise(s) starting with comparison of the quality characteristics of the SBP and the RBP. Demonstration of similarity of an SBP to an RBP in terms of quality is a prerequisite for reducing the nonclinical and clinical data set required for licensure.	Characterization of the quality attributes of the RP should be the first step in guiding the development of the biosimilar. The subsequent comparability exercise should demonstrate structural, functional and clinical similarity. Demonstration of similarity of a biosimilar to an RP in terms of structural and functional aspects, is a prerequisite for establishing comparability, with a tailored clinical data package required as needed.	'stepwise' deleted to reflect the evolution from 'stepwise' to the 'tailored' approach based on the current practices which shows that biosimilar development proceeds in a "concurrent" fashion rather than in a stepwise mode.

Key updates incorporated in the revised GLs

	2009	2022	Reasons for updates
Clinical evaluation	PK, PD, and efficacy studies: The clinical comparability exercise is a stepwise procedure that should begin with PK and PD studies and continue with the pivotal clinical trials. Similar efficacy of the SBP and the chosen RBP will usually have to be demonstrated. In certain cases, however, comparative PK/PD studies may be appropriate. Safety studies: Pre-licensing safety data should be obtained in a sufficient number of patients to characterize the safety profile of the SBP.	PK, PD, and efficacy studies: Clinical studies are a valuable step in confirming similarity. A comparative bioequivalence study involving PK and/or PD comparability is generally required for clinical evaluation. A comparative efficacy and safety trial will not be necessary, if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise. Safety studies: Safety data should be captured throughout clinical development from PK/PD studies and also in clinical efficacy trials when conducted.	Clarified the goal of clinical studies and presented the considerations related to the amount and type of clinical data required for biosimilar evaluation. Articulated that the regulatory perspective about comparative safety and efficacy studies is gradually shifting from a strict inflexible requirement to a case-by-case manner depending on the molecule and the data submitted for demonstration of biosimilarity based on the knowledge and the evidence accumulated to date.

Key updates incorporated in the revised GLs

	2009	2022	Reasons for updates
Clinical evaluation	Immunogenicity: Immunogenicity of biotherapeutic products should always be investigated preauthorization. In the case of chronic administration, one-year data will usually be appropriate pre-licensing to assess antibody incidence and possible clinical implications. Extrapolation of indications: If similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP may be possible.	Immunogenicity: Immunogenicity studies may not be necessary for well-characterized biological substances (for example, insulin, somatropin, filgrastim, teriparatide), where an extensive literature and clinical experience indicate that immunogenicity does not impact upon product safety and efficacy. Authorization of indications: The decision to authorize the requested indications will be dependent upon the demonstration of similarity between the biosimilar and RP.	Clarified that the decision to authorize the requested indications depends on the adequate demonstration of similarity between the biosimilar and RP.

Thank you for attention!

Acknowledgement: WHO drafting group

General comments for entire doc:

1. Dr Patricia Aprea (ANMAT, Argentina)
2. Dr Pekka Kurki (WHO Consultant, Finland)
3. Dr Maria Savkina (the FSBI «SCEEMP» of MOH, Russia)
4. Dr Robin Thorpe (WHO Consultant, UK)

Quality part:

5. Dr Niklas Ekman (FIMEA, Finland): Lead the quality part
6. Dr Sean Barry (HRPA, Ireland)
7. Dr Jeewon Joung (MFDS, Korea)
8. Dr Edwin Nkansah (FDA, Ghana)
9. Dr Junzhi Wang (NIFDC, China)
10. Dr Joel Welch (US FDA, USA)
11. Dr Teruhide Yamaguchi (PMDA, Japan)

Nonclinical part:

12. Dr Hans-Karl Heim (BfArM, Germany)

Clinical part:

13. Dr Elena Wolff-Holz (PEI, Germany): Lead the clinical part
14. Dr Marie-Christine Bielsky (MHRA, UK)
15. Dr Emanuela Lacana (US FDA, USA)
16. Dr Catherine Njue (HC, Canada)
17. *Dr Elkiane Macedo Rama (ANVISA, Brazil)*
18. Dr Meenu Wadhwa (NIBSC MHRA, UK)
19. Dr Jian Wang (HC, Canada)
20. Dr Martina Weise (BfArM, Germany)

WHO Secretariat:

21. Dr Hye-Na Kang (WHO, Switzerland)

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Speaker #3

René Anour, MD, EMA, European Union

René Anour, is a senior clinical expert at the Austrian Medicines & Medical Devices Agency where he coordinates Scientific Advices with industry and serves as lead clinical expert in numerous European Marketing Authorisations. He is furthermore involved in EMA's International Cooperation Platform.

He has more than ten years experience in the Biosimilar area, becoming a member in the EMA Biosimilar Medicinal Product Working Party (EMA-BMWP) in 2020, and recently being elected chairman of this group in July 2023. He is furthermore a member of the HMA Biosimilar Working Group, an initiative to increase uptake of Biosimilars in European countries.

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Biosimilar efficacy clinical trials

What Europe requires

René Anour, AGES, Chair EMA Biosimilar Medicinal Products Working Party (EMA BMWP)

The general philosophy

Clinical trials – a blunt instrument?

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- Aim: to address slight differences shown at previous steps.
- Clinical data cannot be used to justify substantial differences in quality attributes
- The purpose of the efficacy trials is to **confirm comparable clinical performance** of the biosimilar and the reference product.
- Reference: Guideline on similar biological medicinal products (https://www.ema.europa.eu/en/similar-biological-medicinal-products)

When are efficacy trials necessary?

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Per default: required

- adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, by using efficacy endpoints.

- The study population should generally be **representative** of approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences

- In general, an **equivalence design** should be used. The use of a **non-inferiority** design may be acceptable if justified. It is recommended to discuss the use of a non-inferiority design with regulatory authorities

What about safety?

Important throughout clinical development

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- captured during initial PK and/or PD evaluations as part of the pivotal clinical efficacy study.
- normally be collected pre-authorisation
- their amount depending on the type and severity of safety issues known for the reference product. The duration of safety follow-up
- As regards immunogenicity assessment, applicants should refer to existing CHMP guidance (EMEA/CHMP/BMWP/14327/2006 Rev 1, EMA/CHMP/BMWP/86289/2010)

Product specific Guidance

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Most do not strictly require an efficacy trial

- recombinant granulocyte-colony stimulating factor
- low-molecular-weight heparins
- recombinant human insulin and insulin analogues
- interferon beta
- recombinant erythropoietins
- recombinant follicle-stimulating hormone
- somatropin
- **Monoclonal antibodies**

- https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar#-product-specific-biosimilar-guidelines-section

Exceptions to the usual

When can efficacy trials already be omitted?

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- PD markers as established surrogate for efficacy
  - If not reflected in product specific Guidance – seek EMA feedback

- A **comprehensive** and meaningful quality comparability is available and allows for a **tailored clinical approach**

The Tailored Scientific Advice

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Preassessment of Quality to allow for tailoring of clinical program

- EMA offers tailored scientific advice on development programmes of new biosimiliar medicines.

- The tailored procedure advises developers on the studies they should conduct, based on a review of the quality, analytical and functional data they already have available

Reference: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#scientific-advice-on-biosimilars-section

Are there examples for Monoclonals?

Feasibility vs Comprehensiveness

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- 2 Eculizumab Biosimilars (Bekemv and Epysquli)
- Small PD studies (n=42/n=50) in PNH patients.
- Efficacy based on LDH/breakdown of RBC

→ Tailored approach based on feasibility

- https://www.ema.europa.eu/en/medicines/human/EPAR/epysqli
- https://www.ema.europa.eu/en/medicines/human/EPAR/bekemv

The Future

How the need for comparative efficacy trials might evolve

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- It is planned to issue a **concept paper** outlining high level principles regarding a tailored clinical approach based on quality data

- Scope: tbd, but likely focused on Monoclonals

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Speaker #4

Bradley Scott, Ph.D., HC, Canada

Bradley Scott is a Senior Clinical Evaluator at the Biologics and Radiopharmaceutical Drugs Directorate within the Health Products and Foods Branch at Health Canada. He received his B.Sc. degree in biology from the University of Waterloo and his PhD in Cellular and Molecular Medicine from the University of Ottawa where he conducted research for the identification of novel genetic factors involved in chemo- and radio-therapy resistance. He joined Health Canada in 2009 and began working in the area of biologics regulation in 2011. He is actively involved in the review and authorization of biologics for use in hematology and oncology as well as in the regulation of biosimilars. He has authored publications on the Canadian approach to the regulation of biosimilars and is an active member of the biosimilar working group responsible for maintaining Health Canada's guidance relating to biosimilar drug submissions.

Health Canada Santé Canada

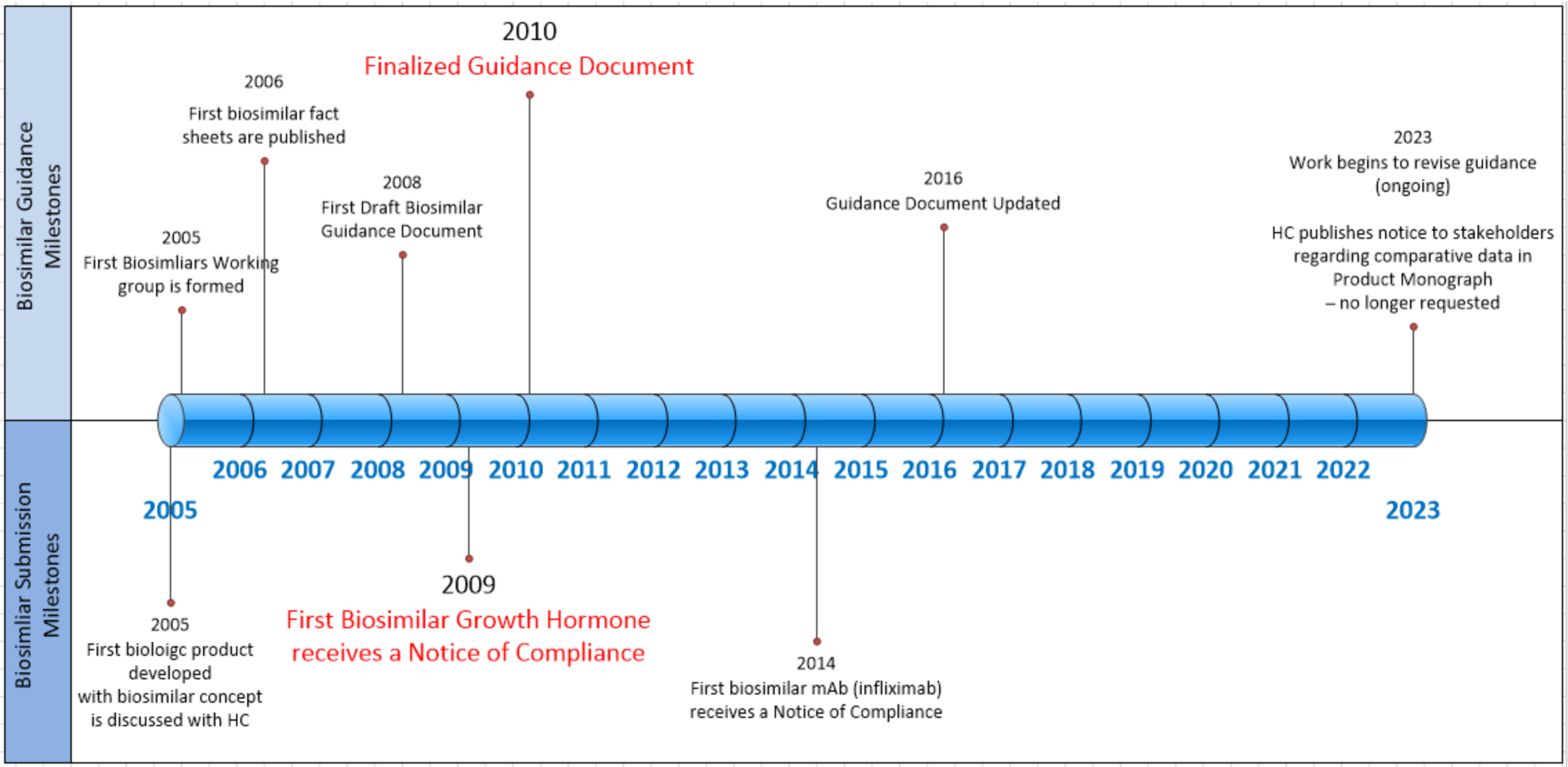
Canada

Biosimilars – Canadian Review and Authorization Experience

Presentation to the IPRF biosimilar workshop

Bradley Scott, PhD
Senior Reviewer, BRDD, HPFB, Health Canada

Brief History of Biosimilars in Canada



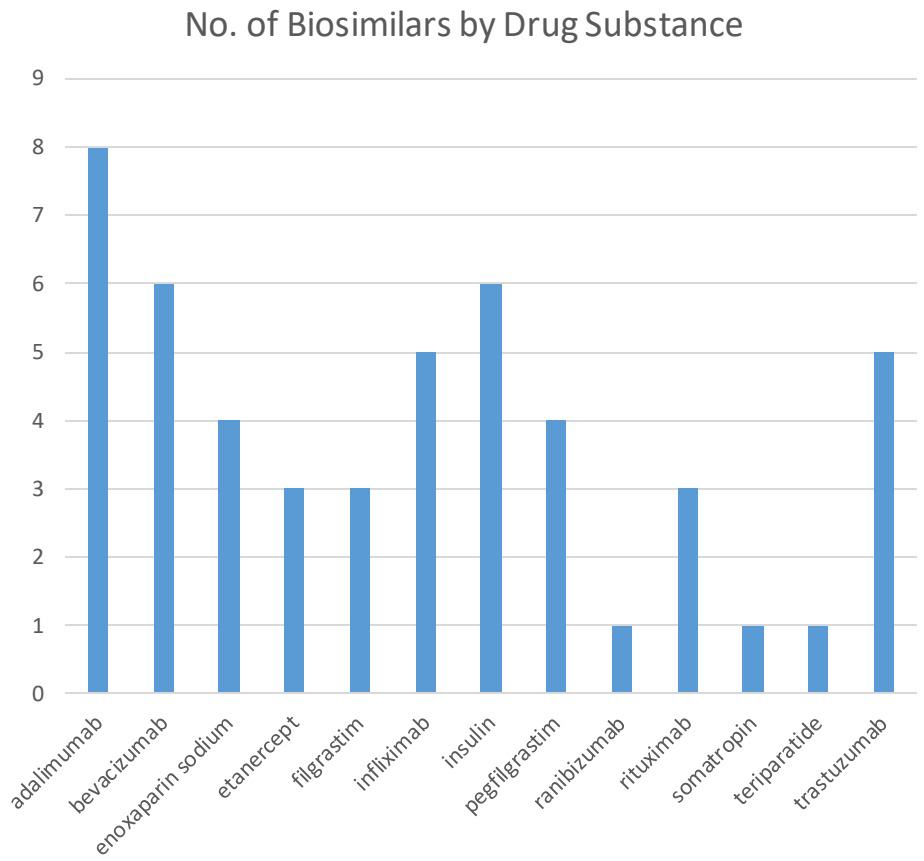
Canadian Biosimilar Authorizations

	Positive Decision	Negative/ Withdrawn	On patent hold	Total
New Biosimilar Submissions	53	10^	5	68

- ^7/10 were withdrawn during review. One of the 7 was part of a parallel filing where the other was issued an NOC. 3 were withdrawn while on patent hold (all were part of parallel filings where one of the filings was issued an NOC)

Biosimilar Authorizations by Drug Substance

- 53 total products representing 16 unique biologics authorized as of 2023
- 6 insulin products representing 4 types of insulin
- Adalimumab currently has the most biosimilar versions of any biologic with 8
- Indications span oncology, autoimmune disease, ophthalmology, diabetes, hematology



Category *insulin* includes insulin aspart, insulin glargine, insulin lispro, insulin (human)

Current Guidance re: Clinical Efficacy Studies

Guidance Document: Information and submission requirements for Biosimilar Biologic Drugs

Current guidance

- *In most cases, a comparative clinical trial(s) is important to rule out clinically meaningful differences in efficacy and safety…*

Exception…

- *A clinical efficacy trial may not always be necessary, e.g., where there is a clinically relevant PD endpoint*

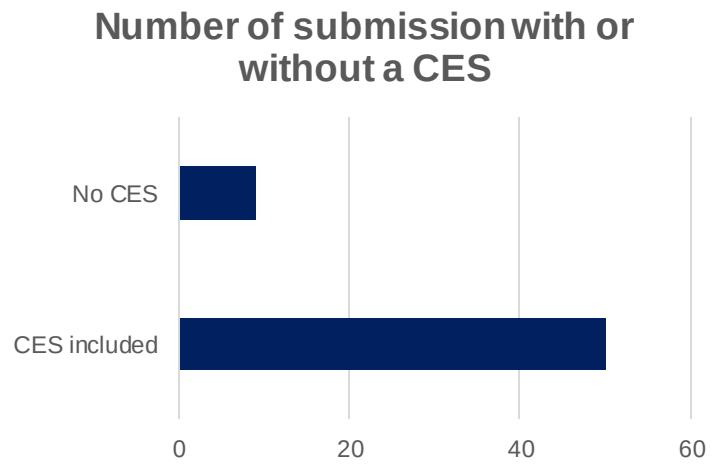
Of note…

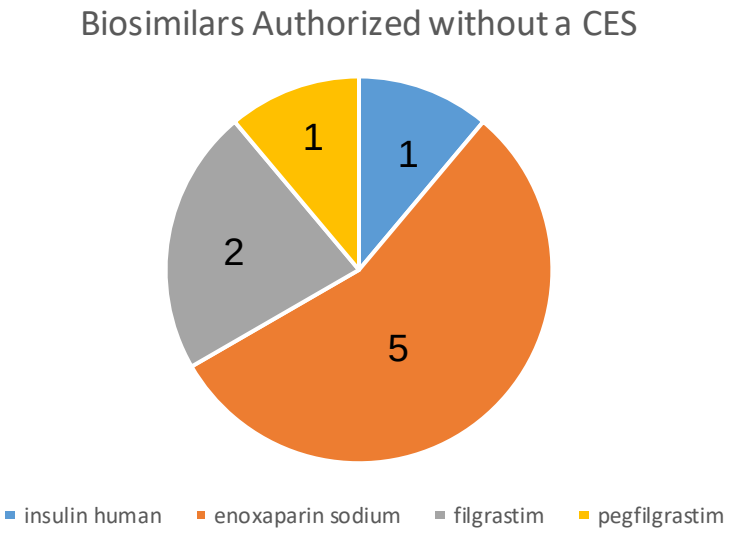
- Industry does not typically engage Health Canada at the biosimilar programme design stage. As such, HC considers the data submitted to determine its adequacy to meet the *regulations*.

Clinical Efficacy Studies (CESs) in Biosimilar Submissions

- To date, the vast majority of biosimilar submissions have included a comparative clinical efficacy study – often using surrogate outcomes as primary endpoints (e.g., overall response rate).

- Submissions without CES studies had characterizable PD endpoints with clinical relevance
  - G-CSFs – Absolute Neutrophil Count (AUEC-ANC)
  - Insulins -- Euglycemic clamp study (AUC-GIR, GIRmax)
  - LMWHs – anti-fXa activity (AUC, Emax)
  - In these cases, the PD marker was expected to be more sensitive to product differences than the relevant clinical outcomes





Observations and Questions re: CESs

- Sensitivity of CESs to product differences is not clear and difficult to establish.
  - known differences (e.g., afucosylation, ADCC activity) vs. residual uncertainty?
  - Is it reasonable to expect that a clinical study could detect a difference where no significant differences are seen in physicochemical or biological activity assays?
- Setting equivalence (or NI) margins depends on prior study data, which might be limited and dated (do the findings hold-up in today's practice settings?)
  - Can create difficulties in margin selection and result interpretation.
- Reporting on primary outcomes and multiple secondary/exploratory endpoints might lead to unwarranted concerns re: biosimilarity despite known limitations (e.g., chance findings, unaddressed multiplicity) with the interpretation of multiple endpoints.
- What action should be taken when numerical differences are observed in various endpoints (e.g., underpowered), e.g., immunogenicity, and how might such action affect healthcare professional and patient uptake of biosimilar products?

Updates

- Health Canada recently updated labelling expectations for biosimilar products advising that comparative studies are no longer expected to appear in Product Monographs. See: Policy Statement
  - In alignment with the SmPC and USPI.
- The Biosimilar Working Group is in the process of revising the guidance including exploring whether there is a continued need for clinical efficacy studies in all but exceptional cases.
- A draft of the revised guidance is expected to be released for consultation in early 2024.
- Comments from the public, including from stakeholders, will be considered before a finalised revision is adopted.

Thank you

Contact info

bradley.scott@hc-sc.gc.ca

BRDD enquiries

Biologic and Radiopharmaceutical Drugs Directorate - Canada.ca

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IPRP International Pharmaceutical Regulators Programme

Speaker #5

Ryosuke Kuribayashi, Ph.D., PMDA, Japan

- Ryosuke Kuribayashi is a Deputy Review Director, Office of Cellular and Tissue-based Products at Pharmaceuticals and Medical Devices Agency (PMDA) in Japan since last year. Currently, he is responsible for the review of biosimilars and the quality of new biopharmaceuticals. Before that, he was in charge of the review of generics in the Office of Generic Drugs from 2013 until 2022. Before that, he served as a researcher, Division of Biological Chemistry and Biologicals at National Institute of Health Sciences, to engage in analytical research on biopharmaceuticals from 2010 through 2012. Before that, he served as a Reviewer within the Office of New Drugs II at PMDA from 2005 through 2010.
- As other activities, he is a member of IPRP Biosimilar WG, Biosimilar cluster, and also ICH M13.

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulatory Experience and Considerations to Date from PMDA

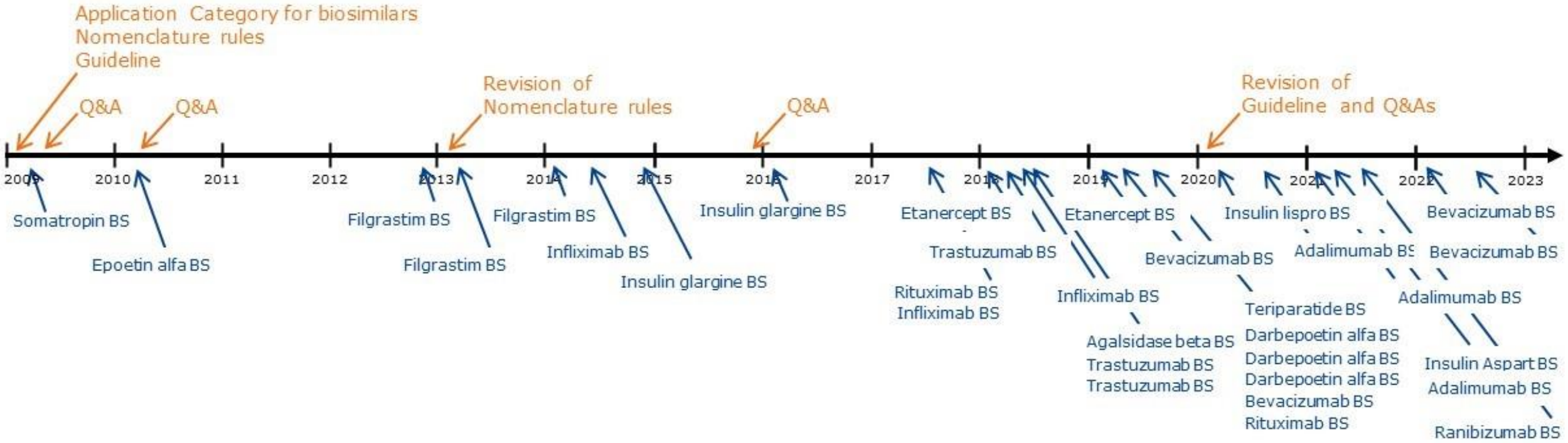
Ryosuke KURIBAYASHI, Ph.D.
Deputy Review Director
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

- Approved biosimilars in Japan
- Approved biosimilar programs which included a comparative efficacy study (CES) , summary of learnings
- Approved biosimilar programs which did not include a CES and why one was not requested
- Any post-marketing/real-world learnings

Approved biosimilars in Japan



32 biosimilars have been approved during the period 2009–2022.

18: mAbs/Fusion proteins　**3**: Cytokines

6: Hormones　**1**: Enzymes

4: EPOs

Approved biosimilar programs which included a CES, summary of learnings

- 23 biosimilars were approved based on comparative analytical studies, a comparative PK study and a CES.
- 7 biosimilars were approved based on comparative analytical studies and a comparative PK/PD study (i.e., without CES).
  3 biosimilars were filgrastim, 4 biosimilars were insulin analogues.
- 1 biosimilar was approved based on comparative analytical studies, a comparative PK study, and a PD study. (i.e., without CES)
  Agalsidase beta BS
- 1 biosimilar was approved based on comparative analytical studies and a CES. (i.e., without comparative PK study)
  Ranibizumab BS

Approved biosimilar programs which included a CES, summary of learnings

- Japanese Biosimilar Guideline

6 Clinical trails

In general, it will be difficult to demonstrate the comparability of a biosimilar with the reference product only based on the data on quality attributes and the results of nonclinical studies. Therefore, the sponsor should evaluate the comparability of a biosimilar through clinical trials. ……. Where pharmacokinetic (PK) and/or pharmacodynamic (PD) studies are sufficient to assure comparability in the clinical endpoint of interest, the afore-mentioned, additional clinical studies to evaluate efficacy might be omitted.

Approved biosimilar programs which did not include a CES and why one was not requested

- 7 biosimilars were approved based on comparative analytical studies and a comparative PK/PD study (i.e., without CES).
  Filgrastim BS, insulin analogues BS

Because PD marker that is a validated surrogate marker for clinical efficacy are available for these products.

Approved biosimilar programs which did not include a CES and why one was not requested

- 1 biosimilar was approved based on comparative analytical studies, a comparative PK study, and a PD study. (i.e., without CES)
  Agalsidase beta BS

Because a biosimilar of agalsidase beta is used against the patients of Fabry disease which was a rare disease.

A sponsor didn't conduct a CES and also a 2 arms comparative parallel-designed PD study due to feasibility, disease property, and mechanism of action (i.e., enzyme replacement therapy).

The study design of PD is single-arm switched therapy from originator to BS (not parallel design).

Mol Genet Metab. 2020;130(3):215-224.

Any post-marketing/real-world learnings

BS is required the implementation of RMP as the “Approval condition: The applicant is required to develop and appropriately implement a risk management plan” based on the domestic notification.

Teriparatide BS SC injection [Mochida] and Infliximab BS IV infusion [NK] were evaluated the safety and efficacy in post marketing surveillance. Approval condition of these two products was removed in 2023.

No safety concern more than originators is found through PMS of BSs so far.

Thank you for your attention!

Ryosuke KURIBAYASHI
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency

IPRP International Pharmaceutical Regulators Programme

Speaker #6

Woo Yong Oh, MFDS, Republic of Korea

Mr. Oh is Acting Director of Recombinant Protein Products Division at the Ministry of Food and Drug Safety (MFDS) in Korea. He has been responsible for reviewing nonclinical, clinical and quality documents of Recombinant Protein Products since 2022.

Before that, he had worked as a senior scientific reviewer in Drug Evaluation Department, followed by his 5 year stint as a researcher in Division of Clinical Research.

In 2001, he joined former MFDS, KFDA and started his career as a scientific officer.

He has worked on the development of many guidelines on the evaluation of drug efficacy and safety.

MFDS' Experience with respect to CES (Comparative Efficacy Studies)

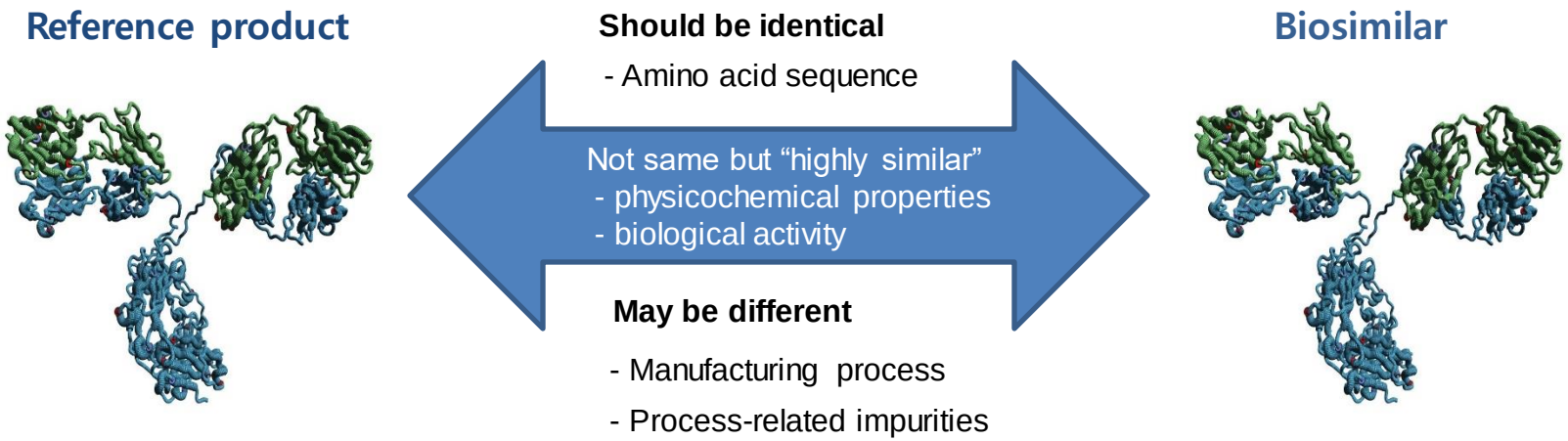
Woo Yong Oh

Recombinant Protein Products Division
National Institute of Food and Drug Safety Evaluation (NIFDS)
Ministry of Food and Drug Safety (MFDS)

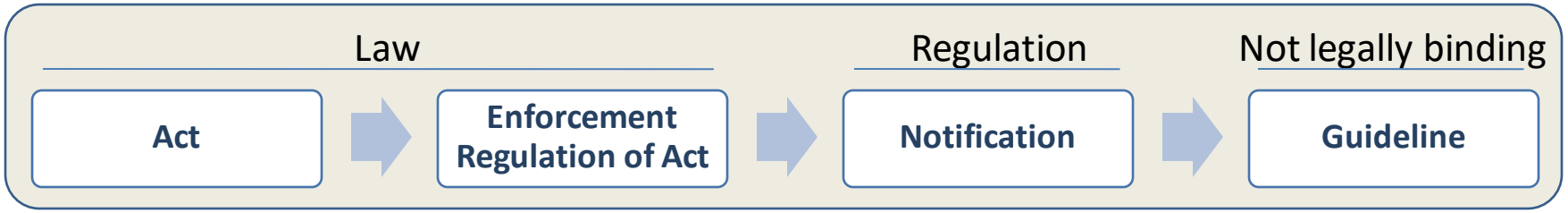
식품의약품안전처
식품의약품안전평가원

Principles of the Biosimilar Evaluation

- The approval of biosimilar products should be based on the **demonstration of similarity** to a chosen reference product.
- The comprehensive characterization and **comparison at quality level with state-of-the-art and orthogonal techniques** should provide a basis for decision of biosimilarity.
- Regulatory decision-making should be based on **totality of evidence** of quality, safety and efficacy data.



Legislative Basis for Regulation of Biosimilar Products



- **The Pharmaceutical Affairs Act (PAA)**
- **Regulation on Safety of Medicinal Products, etc.**
- **Enforcement Regulation of the PAA**
  - ✓ Enforcement Regulation of the Enforcement Decree on the Standards of Facilities of Manufacturers and Importers of Medicinal Products, etc.
- **Notifications**
  - ✓ Regulation on Review and Authorization of Biological Products
  - Clinical study data on a biosimilar product should include information that demonstrate comparability between the biosimilar and the reference product, and also allow for comparative assessment of immunogenicity between them.
  - In principle, clinical study data should be data generated from confirmatory studies.

Legislative Basis of Biosimilar Products Authorization

- **Legislative basis for regulating biosimilar products** was established in September 2009, which was listed in Ministry of Food and Drug Safety (MFDS) Notification.
- **'Guideline on Evaluation of Biosimilar Products'** and **'Questions & Answers regarding Biosimilar Guideline'** were issued in 2009, revised in 2014 & 2022.
  - Currently the guideline is being revised according to WHO's revision of SBP guideline.

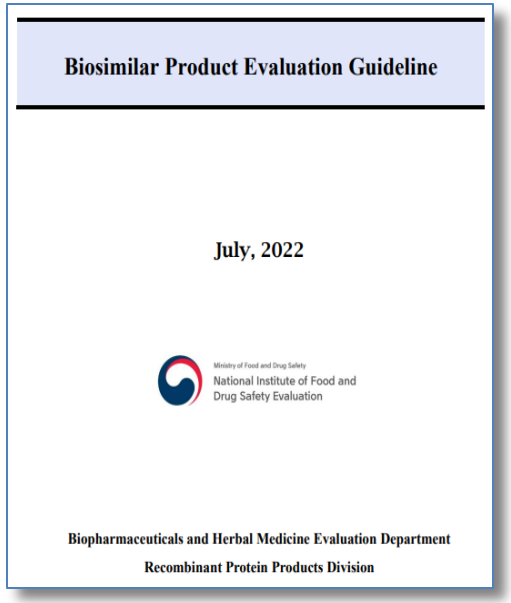
Product-specific Guidelines

- Guideline on non-clinical and clinical evaluation of **erythropoietin** and **somatropin** biosimilar products (2011)
- Guideline on non-clinical and clinical evaluation of **G-CSF** biosimilar products (2012)
- Guideline on non-clinical and clinical evaluation of **monoclonal antibody** biosimilar products (2013)
- Guideline on non-clinical and clinical evaluation of **insulin and insulin analogues** biosimilar products (2015)
- Guideline on non-clinical and clinical evaluation of **r-hFSH** biosimilar products (2022)
- Guideline on non-clinical and clinical development of similar biological medicinal products containing **interferon beta**(2023)

Clinical Data Considerations for Biosimilar Evaluation

- A PK and /or PD comparability study are/is required for clinical evaluation.
- **Comparative efficacy study is generally expected** but it may not be necessary if sufficient evidence biosimilarity can be drawn from analytical and in vitro pharmacological studies and comparative PK/PD studies in certain types of products.

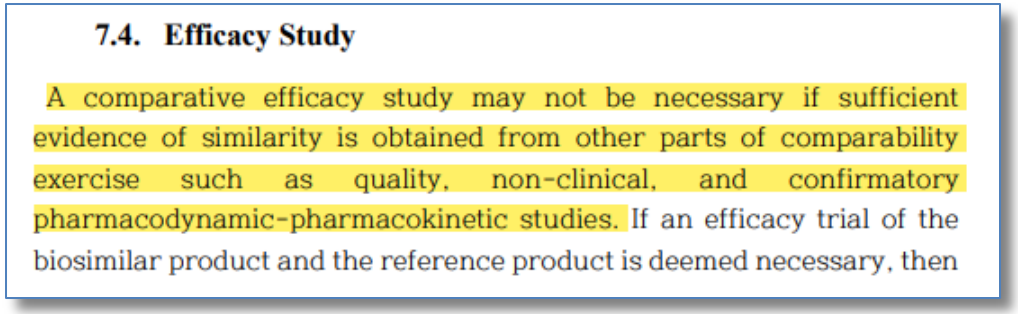
  - Example : G-CSF, teriparatide, etc.


Biosimilar Product Evaluation Guideline

July, 2022

Ministry of Food and Drug Safety
National Institute of Food and Drug Safety Evaluation

Biopharmaceuticals and Herbal Medicine Evaluation Department
Recombinant Protein Products Division


7.4. Efficacy Study

A comparative efficacy study may not be necessary if sufficient evidence of similarity is obtained from other parts of comparability exercise such as quality, non-clinical, and confirmatory pharmacodynamic-pharmacokinetic studies. If an efficacy trial of the biosimilar product and the reference product is deemed necessary, then

Biosimilar Products Developed in Korea

No	Company	Drug name	Active ingredient	Indication	Approval date	EMA Approval	FDA Approval
1	Celltrion	Remsima*, ** 100mg	Infliximab	Rheumatoid Arthritis	Jul 20, 2012	Remsima (Sep 10, 2013)	Inflectra (Apr 5, 2016)
2	Celltrion	Herzuma* 150,440mg	Trastuzumab	Breast Cancer	Jan 15, 2014	Herzuma (Feb 9, 2018)	Herzuma (Dec 14, 2018)
3	Samsung Bioepis	Etoloce 50mg**	Etanercept	Rheumatoid Arthritis, Psoriasis	Sep 7, 2015	Benepali (Jan 14, 2016)	Eticovo (Apr 25, 2019)
4	Samsung Bioepis	Remaloce 100mg**	Infliximab	Rheumatoid Arthritis	Dec 4, 2015	Flixabi (May 26, 2016)	Reneflexis (Apr 21, 2017)
5	Celltrion	Truxima	Rituximab	Rheumatoid Arthritis, Lymphoma	Jul 16, 2015	Truxima (Feb 17, 2017)	Truxima (Nov 28, 2018)
6	Samsung Bioepis	Adalloce PFS 40mg, Adalloce PEN 40mg	Adalimumab	Rheumatoid Arthritis, Psoriatic Arthritis	Sep 20, 2017, Jul 03, 2020	Imraldi (Aug 24, 2017)	Hadlima (Jul 23, 2019)
7	Samsung Bioepis	Samfenet 150mg Samfenet 440mg	Trastzumab	Breast Cancer, Gastric cancer	Nov 8, 2017, Oct 14, 2020	Ontruzant (Nov 15, 2017)	Ontruzant (Jan 18, 2019)

** PMDA approved, ** HC approved*

Biosimilar Products Developed in Korea

No	Company	Drug name	Active ingredient	Indication	Approval date	EMA Approval	FDA Approval
8	LG Chem Ltd.	Eucept* Prefilled Syringe	Etarnercept	Rheumatoid Arthritis, Psoriatic Arthritis, etc.	Mar 16, 2018		
9	Chongkundang	Nesbell*	Darbepoetin alfa	Anemia	Nov 29, 2018		
10	Panzen	Panpotin	Epoetin alpha	Anemia	Nov 28, 2019		
11	Samsung Bioepis	Onbevzi	Bevacizumab	Colorectal cancer, Breast cancer, NSCLC, RCC, etc.	Mar 11, 2021	Aybintio (Aug 19, 2020) Onbevzi (Jan 11, 2021)	-
12	Celltrion, Inc.	Yuflyma PFS, PFN 40mg, Yuflyma PFS, PFN 80mg	Adalimumab	Rheumatoid Arthritis, Psoriatic Athritis, etc.	Oct 15, 2021 Jun 15, 2022	Yuflyma (Fab 11, 2021)	Yuflyma (May 23, 2023)
13	Samsung Bioepis	Amelivu	Lucentis	Age-related Macular Degeneration, etc.	May 13, 2022	Byooviz (Aug 18, 2021)	Byooviz (Sep 17, 2021)
14	Celltrion, Inc.	Vegzelma	Bevacizumab	Colorectal cancer, Breast cancer, NSCLC, RCC, etc.	Sep 28, 2022	Vegzelma (Aug 17, 2022)	Vegzelma (Sep 27, 2022)
15	Chongkundang	Lucenbies 10mg, PFS	Lucentis	Age-related Macular Degeneration, etc.	Oct 20, 2023 May 19, 2023		

* *PMDA approved*

Biosimilar Products Imported from Global Companies

No	Company (developed by)	Drug name	Active ingredient	Indication	Approval date
1	Scigen Korea	SciTropin A	Somatropin	Growth hormone deficiency, etc.	Jan 28, 2014
2	Green Cross (Biocon)	Glarzia	Insulin glargine	Diabetes	Mar 07, 2018
3	Daewon Pharm (Gedeon Richter)	Terrosa	Teriparatide	Osteoporosis	Oct 29, 2019
4	Alvogen Korea (Mylan/Biocon)	Ogivri	Trastuzumab	Breast Cancer, Gastric cancer	Aug 26, 2020
5	Yooyoung Pharm (Gedeon Richter)	Bemfola	Follitropin alfa	IVT/ET, GIFT ZIFT, ICSI etc.	Oct 29, 2020
6	Pfizer Korea	Zirabev	Bevacizumab	Colorectal cancer, Breast cancer, NSCLC, RCC, etc.	May 17, 2021
7	**Phambio Korea. Inc.**	**Bonsity**	**Teriparatide**	**Osteoporosis**	**Nov 16, 2021**
8	Alvogen	Alymsis	Bevacizumab	Colorectal cancer, Breast cancer, NSCLC, RCC, etc.	Jan 19, 2022

Phase 3 Comparative Efficacy Studies of Biosimilars (2012~2023.06)

Approved Products

- ✓ 15 products by domestic companies
- ✓ 8 products by foreign companies

Phase 3 Comparative Efficacy Studies

- ✓ Mostly, one comparative efficacy study conducted for each product : randomized, active-controlled
- ✓ Sample size of around 100~900 subjects
- ✓ Equivalence or non-inferiority of the biosimilar to the reference product confirmed
- ✓ Sufficient statistical power secured
- ✓ Primary efficacy endpoint
  - Oncology drugs (ORR, CR), rheumatoid arthritis (ACR20 responder ratio, DAS28-ESR score changes), anemia (changes in hemoglobin levels), macular degeneration (changes in best corrected visual acuity or the ratio of patients showing vision loss for below the row of OO letters in eye chart), etc.

Phase 3 Comparative Efficacy Studies of Biosimilars (2012~2023.06)

- **Biosimilar, having failed comparative efficacy study but approved**

  ✓ API :Trastuzumab

  ✓ Clinical study design : Randomized, double-blind, active-control

  ✓ Primary efficacy endpoint : Complete response rate

  ✓ Key outcomes : Differences in pathological CR rates failed to demonstrate the pre-specified equivalence.

  However, an analysis, conducted excluding patients given an ADCC variable reference product, showed that the pre-specified equivalence margin was met.

- **Biosimilar, approved with PK comparability data only**

  ✓ API : Teriparatide

  ✓ Clinical study design : Randomized, double-blind, single-dose, cross-over

  ✓ Primary efficacy endpoint : AUCt, Cmax

  ✓ Key outcomes : Equivalence was demonstrated by fulfilling the pre-specified equivalence margin (80~125%).

Post-marketing Safety Management of Biosimilars

▪ Regulations on Re-examination of Biosimilars

✓ Enforcement Regulation on the Safety of Drug, Etc. Article 4

- In the case of drugs designated by Minister of MFDS such as new drugs and orphan drugs (refers to drugs, which must be urgently introduced as there are no other alternative drugs and have been designated by Minister of MFDS, and this applies hereunder), etc., a comprehensive drug safety management plan (hereinafter referred to as the 'risk management plan'), which includes risk reduction measures as prescribed by Minister of MFDS such as a user guide for patients and measures to assure safe use thereof

✓ **Enforcement Regulation on the Safety of Drug, Etc. Article 22**

- Products for which PMS shall be performed for 4 years after approval for manufacturing, marketing and import

a. Ethical drugs with the same active ingredient and administration route as an already approved drug but with additional efficacy and effectiveness that are clearly different

b. Other drugs acknowledged to require PMS by Minister of MFDS : *Biosimilar, etc.*

Post-marketing Surveillance of Biosimilars

On-going Post-marketing Surveillance of Biosimilars

✓ Post-marketing requirement for re-examination of biosimilars : 23 products

✓ PMS: Completed for 9 products, Underway for 14 products

✓ AE occurrences, etc. reflected into Precautions for Use following the completion of the re-examination of biosimilars

- The Re-examination conducted in 000 participants for 0 years as part of the PM requirements found that the AE incidence rate was 00% regardless of causality (00/000, 00 cases). serious drug adverse reactions (SDARs) and unexpected DARs for both of which causality cannot be ruled out are listed in the table below.

Frequencies	*Organ System*	*Serious drug adverse reactions or unexpected drug adverse reactions*
	System Organ Class	*Adverse event*

✓ The sample size : Around 180~1,400 persons

✓ No emergent safety concerns identified for the biosimilars that have completed PMS.

Conclusions and Key Takeaways

▪ Phase 3 Comparative Efficacy Studies

✓ Comparative efficacy studies conducted for 22 out of the total 23 locally manufactured and imported biosimilars except Teriparatide

(Comparative efficacy studies)

- API: Trastuzumab, Rituximab, Bevacizumab, Ranibizumab, Infliximab, Etanercept, Adalimumab, Darbepoetin-alpha, Epoetin-alpha, Somatropin, Insulin Glargine, Follitropin-alpha

(Pharmacokinetic studies)

- API: Teriparatide

▪ Post-marketing Surveillance

✓ For the 23 locally manufactured and imported biosimilars, Post-marketing Re-examination has been completed or is underway as part of their post-approval commitments in accordance with the MFDS regulations on post-marketing safety management.

- Post-marketing Re-examination competed for 9 biosmilars: The 4 year post-approval follow-up has identified no new safety concerns for serious DARs or unexpected DARs in the sample size of around 180~1,400 persons.

IPRP International Pharmaceutical Regulators Programme

Speaker #7

Stacey Ricci, Sc.D., FDA, United States of America

For the past 18 years, Dr. Ricci's work at FDA has focused on the scientific and regulatory review of therapeutic protein products. In her current role as Director of the Scientific Review Staff in the Office of Therapeutic Biologics and Biosimilars (OTBB), Dr. Ricci leads a multidisciplinary team of scientists, clinicians, pharmacists, and project managers who oversee the review of biosimilar and interchangeable products at all stages of development and who advance biosimilar policy and scientific standards by conducting regulatory science research, facilitating scientific dialogue (within FDA and through stakeholder engagement), developing and contributing to guidance and rulemaking, and providing educational and training opportunities. Prior to joining FDA in 2005, Dr. Ricci completed post-doctoral research at the University of Pennsylvania, received her Doctor of Science degree from Tulane University, and Master of Engineering and Bachelor of Science degrees from Cornell University.

Comparative Efficacy Studies:
Biosimilar Approvals in the United States

Increasing the Efficiency of Biosimilar Development Programs—
Reevaluating the Need for Comparative Clinical Efficacy Studies

Public Session - September 12, 2023

M. Stacey Ricci, M. Eng., Sc.D.
Director, Scientific Review Staff
Office of Therapeutic Biologics and Biosimilars
Office of New Drugs | Center for Drug Evaluation and Research

U.S. FOOD & DRUG ADMINISTRATION

Overview

- Where are we now and how did we get here?
- Where do we want to go and how to get there?

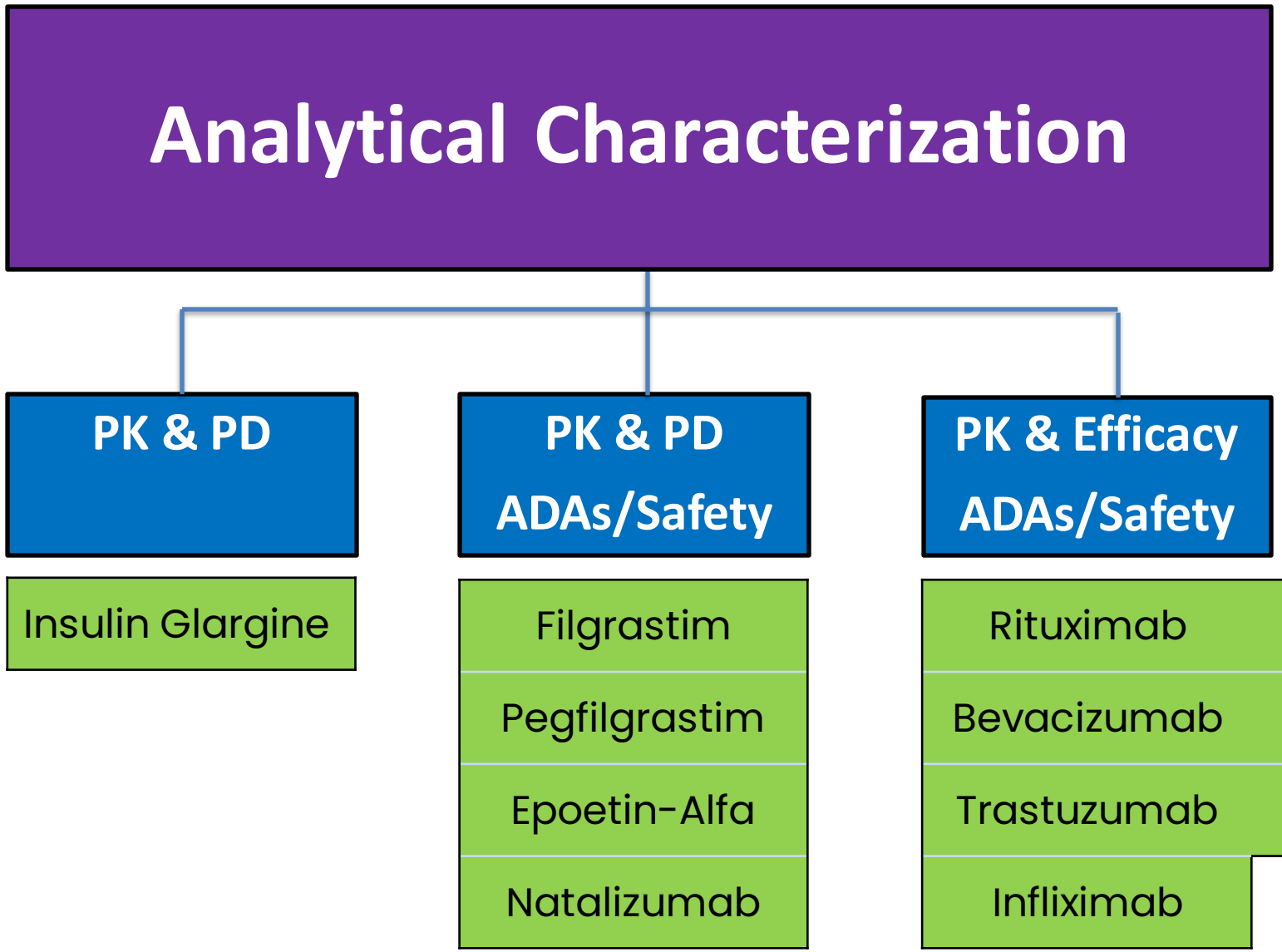
Product Class		U.S. Approvals (42)
Supportive Care	Filgrastim	B B B
	Pegfilgrastim	B B B B B B
	Epoetin-Alfa	B
Oncology	Rituximab	B B B
	Bevacizumab	B B B B
	Trastuzumab	B B B B B
Autoimmune	Infliximab	B B B B
	Etanercept	B B
	Adalimumab	B I B B B B B B B
	Insulin Glargine	I I
	Natalizumab	B
Ophthalmology	Ranibizumab	B I

42 biosimilars approved to 12 different reference products

B Biosimilar

I Interchangeable Biosimilar

Comparative Data Supporting Approval



PK, PD, efficacy:
statistical comparisons

ADAs and safety:
descriptive comparisons

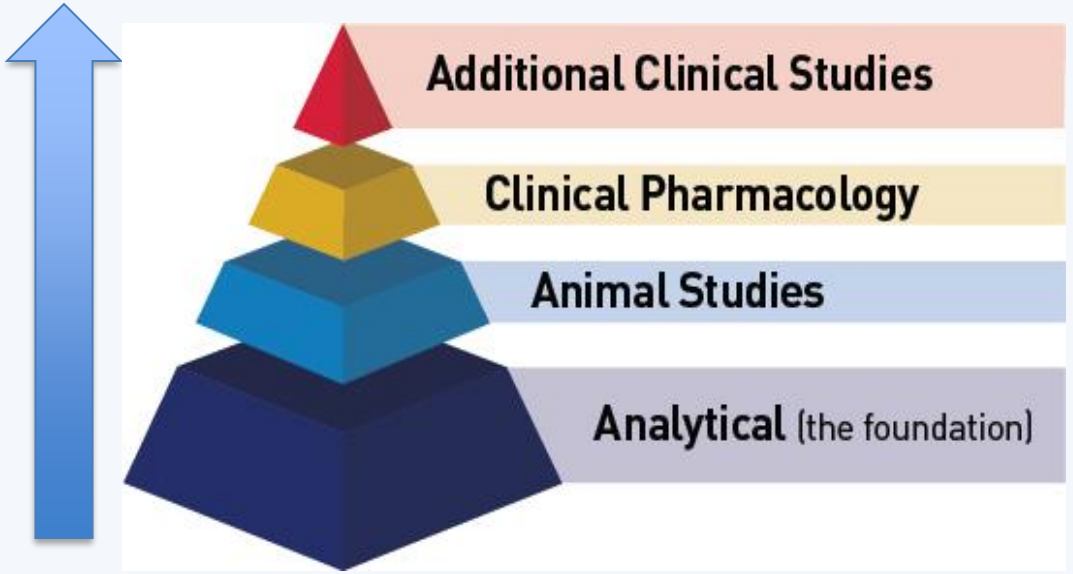
Stepwise development approach recommended…

BPCIA grants FDA the authority to approve biosimilar and interchangeable products

FDA publishes guidance on recommended stepwise approach for biosimilar development (analytical, animal, clinical studies)

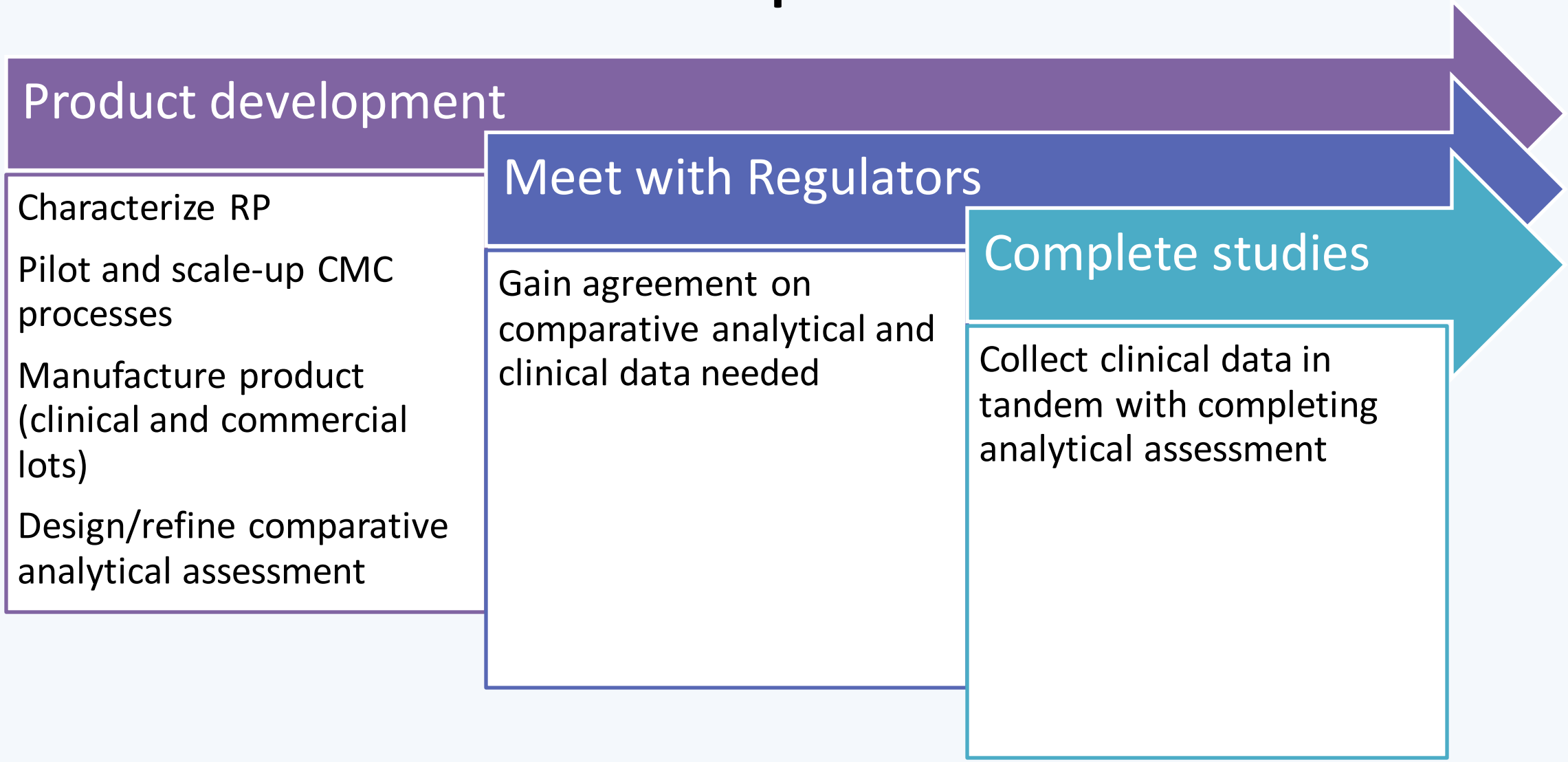
First biosimilar approved in the U.S.

2010 2011 2012 2013 2014 2015



… but not easy to put into practice

Biosimilar Development Timeline



Factors Contributing to Clinical Data Expectations

- Stepwise approach not very practical
  - assumes that comparative analytical data package can be sufficiently complete before making decisions about clinical program
- Newness of the biosimilar program
- Lack of experience using biosimilars—theoretical concerns about safety and efficacy
- Clinical efficacy endpoint historically expected based on familiarity and confidence in new drug development paradigm
  - hypothesis testing based on statistical equivalence establish safety and efficacy

Streamlining Clinical Data Expectations

- Increase confidence in comparative analytical data
  - Focused efforts needed to enhance understanding that robust structural and functional analytical comparisons demonstrating products are “highly similar” can provide assurance that a biosimilar will have the same clinical performance as its reference biologic
  - Highlight that clinical endpoints are not as sensitive as analytical data to detect differences
- Develop risk-based criteria to justify when a limited clinical assessment (e.g., a single dose PK study in healthy subjects) is sufficient to complement the comparative analytical data needed to demonstrate biosimilarity
- Update scientific recommendations in guidance, as appropriate

Thank You

Visit **www.FDA.gov/biosimilars**

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Panel Discussion

- Regulatory Experience and Considerations to Date (110 min) Moderated by Ali Al Homaidan, SFDA
- Panelists
  - MHRA: Marie-Christine Bielsky
  - WHO: Hye-Na Kang, Eun Kyung Kim
  - EMA: René Anour, Steffen Thirstrup
  - Health Canada: Bradley Scott
  - PMDA: Ryosuke Kuribayashi, Yasuhiro Kishioka, Kenji Hayamizu
  - MFDS: Woo Yong Oh, Mi Ryeong Jin, Soo Jeong Cheon, Hea Jeong Doh
  - US FDA: Stacey Ricci, Emanuela Lacana

IPRP International Pharmaceutical Regulators Programme

Panel

Possible Questions

- What do you think are the common reasons CES have been utilized widely in biosimilar development programs so far?
- In your experience, are CES results being used to resolve residual uncertainty arising from the comparative analytical assessment, or are CES typically considered on their own?
- What information can sponsors provide that would be most helpful in supporting a determination that a CES is not needed for a given development program?

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Closing Remarks