



Biosimilar Regulation and Guidelines in Japan

HAYAMIZU Kenji, Ph.D

Reviewer

Office of Cellular and Tissue-based products

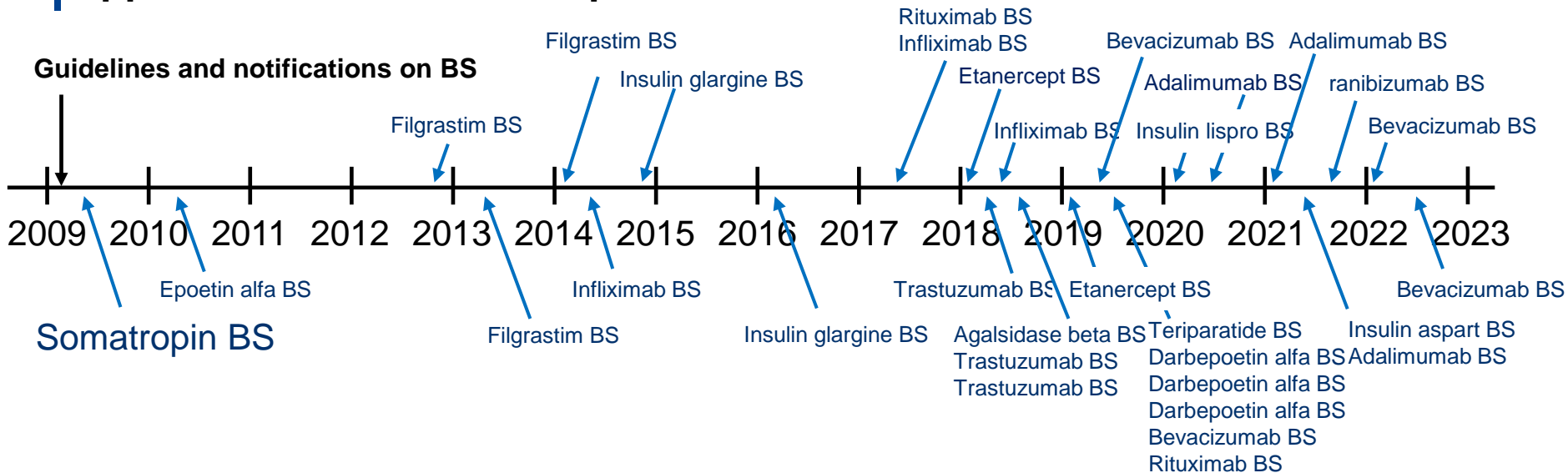
Pharmaceuticals and Medical Devices Agency (PMDA)

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

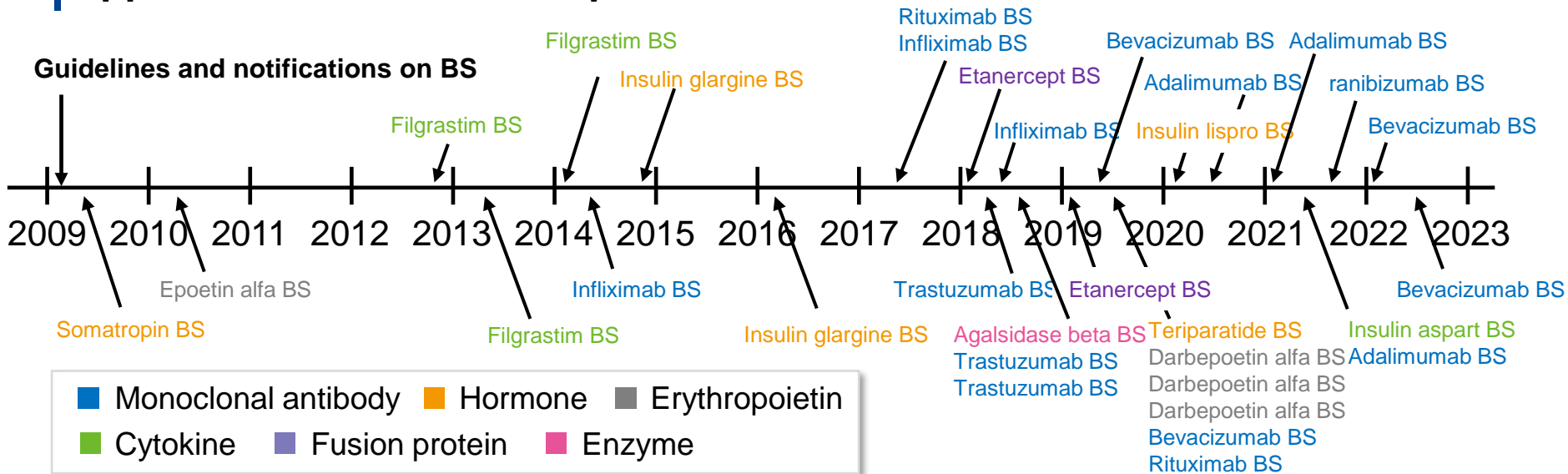
1. Introduction
 - Approved Biosimilars
 - Development Status
 - Japanese Guidelines
2. Guidelines on Biosimilars
 - General Principles in the Development of Biosimilars
 - Frequently Asked Questions
3. A Recent Topic in Biosimilars

Approved Biosimilars in Japan



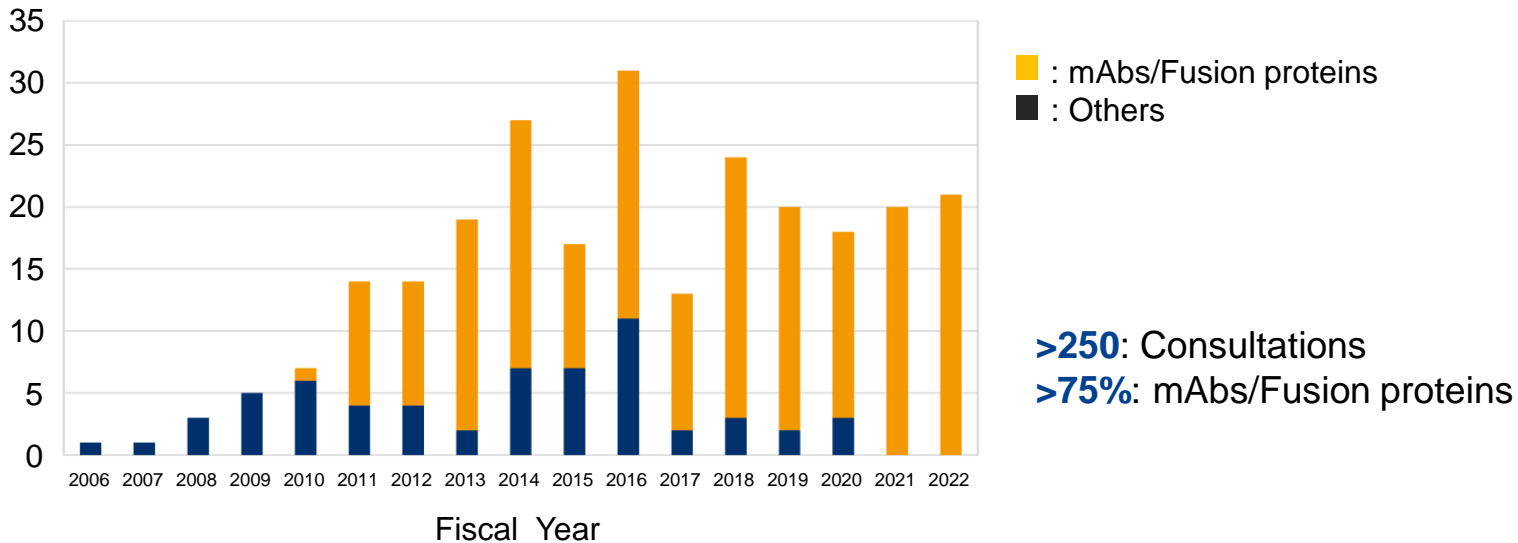
- The first approval of a biosimilar product in Japan was somatropin BS subcutaneous injection [Sandoz] in 2009.
- 32 biosimilar products were approved during the period 2009–2022.

Approved Biosimilars in Japan



- There are six types of biosimilars, namely mAb, hormone, erythropoietin, cytokine, fusion protein, and enzyme.
- In recent years, antibodies make up more than half of newly developed biosimilars.

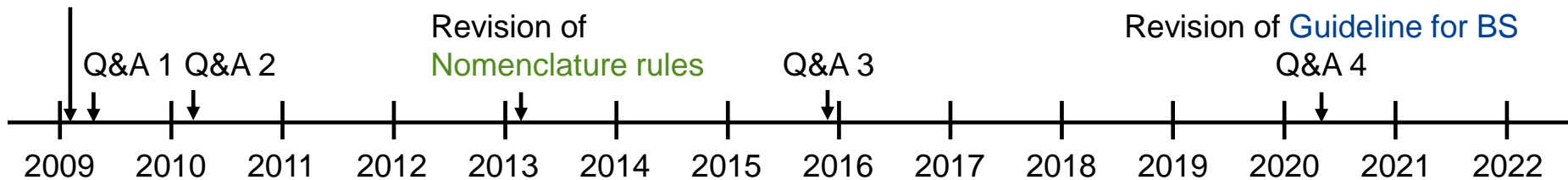
Number of Consultation for Biosimilars



- More than 250 consultations had been implemented by 2022.
- Interest in biosimilar development continued to remain high, and several biosimilars have been under review in Japan.

Guideline and Notifications for Biosimilars in Japan

- Notification: Application Category for biosimilars
- **Guideline on BS**
- **Notification: Nomenclature rules**



- **Marketing Approval for Biosimilars**
(PFSB Notification 0304004 / March 4, 2009)
- **Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars**
(PSEHD/PED Notification No. 0204-1 / February 4, 2020)
- **Nonproprietary Name and Drug Name of Biosimilars**
(PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013)

Guideline for Biosimilars

- **Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars**
(PSEHD/PED Notification No. 0204-1 / February 4, 2020)
- **Questions & Answers regarding Guideline**
(PFSSB/ELD Administrative Notice / February 4, 2020)

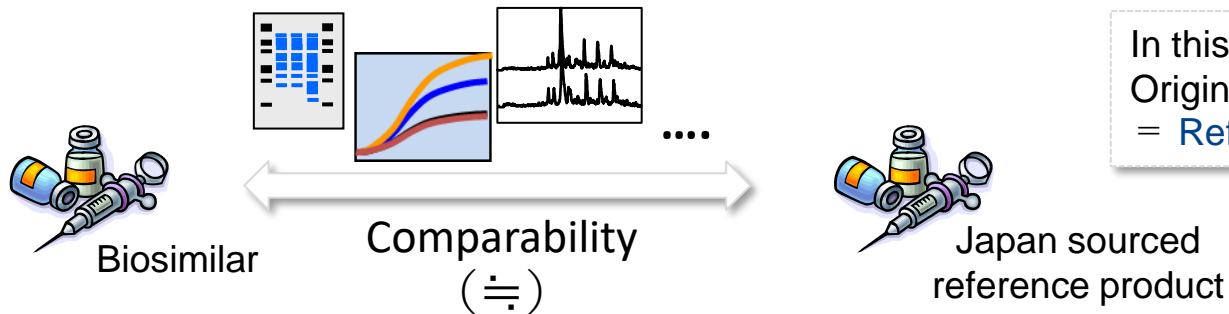
(These revised guidelines and Q&A in English are in preparation.)

- These guidelines and QA address the points to be considered during the development of biosimilars and clarifies the data that should be submitted in biosimilar applications.

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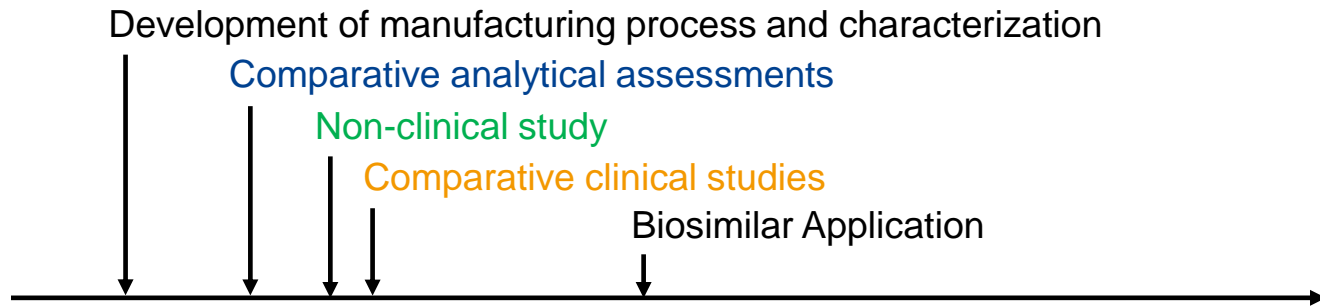
General Principles in the Development of Biosimilars (1)



- A biosimilar is a product comparable with regard to quality, safety, and efficacy to a original biopharmaceutical (a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients, which is developed by a different company).
- In the development of biosimilar products, “comparability” means that the quality attributes of a biosimilar are highly similar to those of its reference product and it can be scientifically justified that any differences in the quality attributes have no adverse impact on clinical safety or efficacy based on non-clinical and clinical trial results.

General Principles in the Development of Biosimilars (2)

Development flow of biosimilars

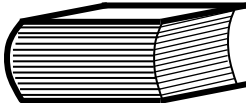
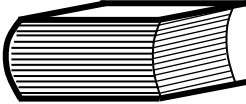
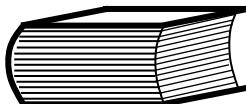
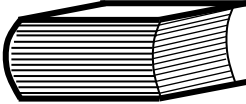



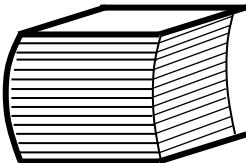


- The sponsor should demonstrate the comparability of the proposed product with its reference product through **quality**, **non-clinical** and **clinical** comparisons.
- The extent and necessity of **non-clinical** and **clinical study** data required for the demonstration of comparability will differ depending on the extent to which similarity of the biosimilar with its reference product has been demonstrated by a scientific and rational evaluation of the quality attributes in the **comparative analytical assessment**.

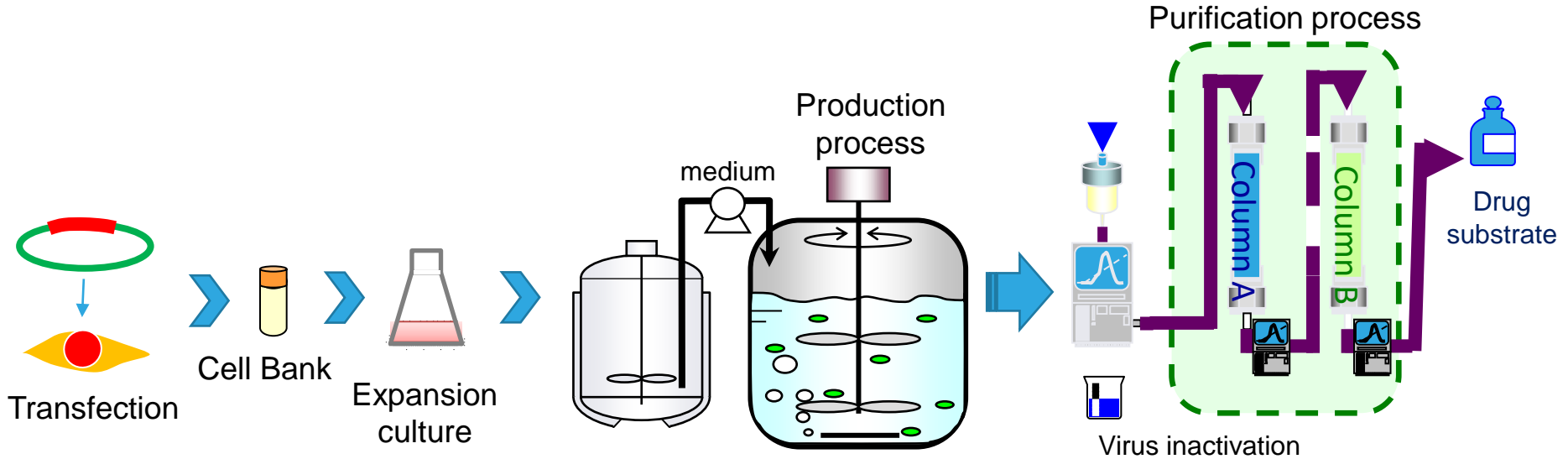
Data Requirement of Biosimilars

Biosimilar Application

New drug Application

← Development of manufacturing process and characterization		≡	
← Comparative analytical assessments <ul style="list-style-type: none"> • Structural and physiochemical properties • Biological activities (<i>in vitro</i> assays) • Process related impurities 		≡	
← Non-clinical study <ul style="list-style-type: none"> • <i>in vitro</i> and <i>in vivo</i> assays • Toxicological studies 		≡	
← Comparative clinical studies <ul style="list-style-type: none"> • Clinical pharmacology • Safety and efficacy • Immunogenicity 		≡	
← Biosimilar Application			

General Principles - Comparative Analytical Assessments (1)



- The manufacturing process of a biosimilar is **independently** developed by the sponsor. Therefore, there will be many differences in the manufacturing process between the biosimilar and its reference product.

General Principles - Comparative Analytical Assessments (2)

Examples of differences	Examples of quality attributes that may be affected
Host cell line ex. NSO cells ⇒ CHO cells	<ul style="list-style-type: none"> • Process-related impurities (Host cell proteins, Host cell DNA, <i>etc.</i>) • Post-translational modifications (such as glycosylation) , <i>etc.</i>
Culture conditions ex. pH, Incubation temperature, Dissolved oxygen level, Glucose level, Incubation period, <i>etc.</i>	<ul style="list-style-type: none"> • Post-translational modifications (Oxidation, Deamination, Glycation, <i>etc.</i>) • Heterogeneity of glycosylation (N-linked glycan profile, N-linked glycan binding site, <i>etc.</i>) , <i>etc.</i>
Purification process	<ul style="list-style-type: none"> • The residual amount of impurities (Product-related impurities and Process-related impurities) • Virus removal ability of the manufacturing process, <i>etc.</i>

- The comparability of the biosimilar to its reference product should be evaluated taking into full consideration such differences in the manufacturing processes of each product.

General Principles - Comparative Analytical Assessments (3)

- The degree of similarity of quality attributes should be clarified by comparing multiple lots of the drug substance or the drug product. The impact of observed differences on efficacy and safety should be assessed, and non-clinical and clinical studies should be designed and conducted based on the results of that assessment.
 - Analytical method
 - ✓ It is important to use analytical methods with sufficient performance in order to detect differences in quality attributes between the biosimilar and its reference product.
 - ✓ It is advisable to perform multidimensional evaluations by using multiple orthogonal analytical methods having different principles in order to analyze complicated quality attributes such as aggregates.

General Principles - Comparative Analytical Assessments (4)

- Evaluation items
 - ✓ It is necessary to evaluate the following quality attributes related to structural and physico-chemical properties, biological activities, and impurities.

	Examples of quality attributes
Structural and physico-chemical properties	Amino acid sequence, Disulfide bonds, Glycan structures, High order structure, other post-translational modifications, <i>etc.</i>
Biological activities	Antigen-binding affinity, Neutralization activity, ADCC activity, CDC activity, Binding activity with Fcγ receptors, compliment C1q, and FcRn, <i>etc.</i>
Impurities	Product-related impurities such as aggregates and truncated forms, <i>etc.</i> Process-related impurities such as substances which commonly used in manufacturing processes, <i>etc.</i>

General Principles - Comparative Analytical Assessments (5)

- Comparison of biological properties
 - ✓ In general, in the case of a biosimilar of antibodies, the following quality attributes should be compared with those of its reference product.

	Examples of quality attributes
Biological activities	Antigen-binding affinity, Neutralization activity, ADCC activity, CDC activity, Binding activity with Fcγ receptors, compliment C1q, and FcRn, <i>etc.</i>

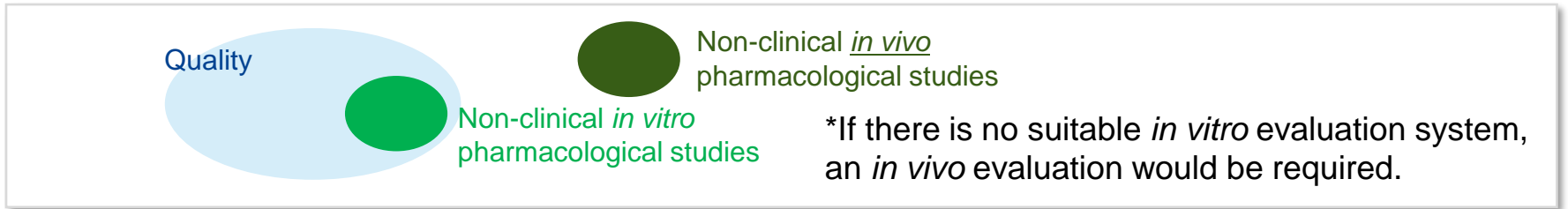
- ✓ In the case of a protein with multiple functional domain structures, the functions of the whole molecule can be compared by comparing the biological activities of each domain.
- ✓ If differences are found in the comparison of structural and physico-chemical properties that may affect biological activity, the extent to which the differences affect biological activity should be clarified and the impact on efficacy and safety should be considered.

General Principles – Non-clinical Study (1)

- The quality attributes of biosimilar should be fully evaluated prior to conducting non-clinical studies. In addition, non-clinical studies should be rationally and appropriately designed with reference to the results of characterization of the biosimilar itself and comparison with the quality attributes of its reference product.
 - Non-clinical pharmacokinetics study
 - ✓ The heterogeneity of glycan chains in some glycoprotein products may have a significant impact on *in vivo* pharmacokinetics. When *in vitro* activity may not correlate with clinical efficacy, as is the case with such proteins, It would be useful to compare the non-clinical pharmacokinetics between the biosimilar and its reference product as part of the comparability study.

General Principles – Non-clinical Study (2)

- Non-clinical Pharmacology study

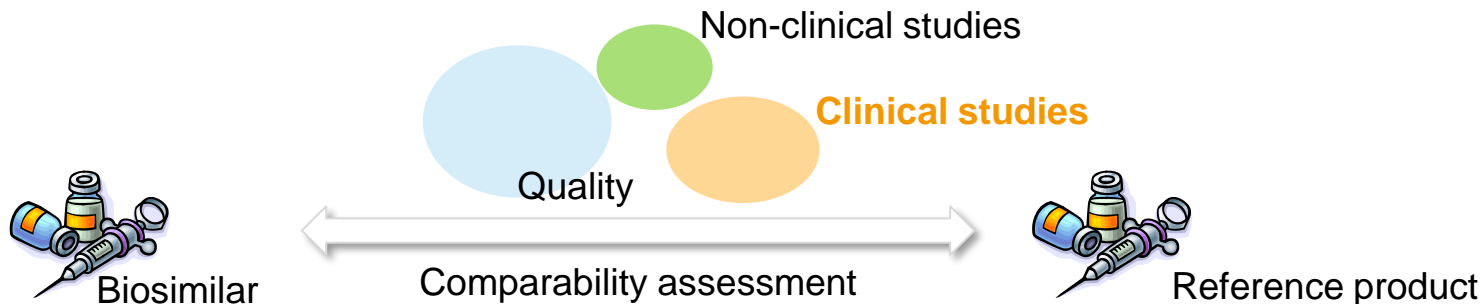


- ✓ If a comparison of *in vitro* biological activity (e.g., cell-based studies, receptor binding activity) that is closely related to clinical efficacy is required and the relevant evaluations taking the mechanism of action into account are performed as part of comparative quality assessments, these studies can be applied as a non-clinical pharmacology studies.
- ✓ Where the similarity of bioactivity between the biosimilar and its reference product is fully evaluated by *in vitro* comparability studies, *in vivo* comparative pharmacology studies may not be necessary.

General Principles – Non-clinical Study (3)

- Non-clinical safety studies
 - ✓ If a biosimilar has a high similarity to its reference product and the sponsor can sufficiently explain that there are no safety concerns in conducting clinical studies, non-clinical safety studies can be omitted.
 - ✓ On the other hand, where there are safety concerns that differ from those of its reference product based on the quality and pharmacology studies of the biosimilar, non-clinical safety studies should be conducted based on these information with reference to the ICH S6 guideline and others.

General Principles – Comparative Clinical Study (1)



- The sponsor should evaluate the comparability of a biosimilar through clinical trials, because it is difficult to demonstrate the comparability between the biosimilar and the reference product only based on the data from quality and non-clinical studies.
- Necessary and appropriate clinical studies should be designed to assess the comparability of the biosimilar with its reference product in terms of clinical efficacy and safety, taking into account comprehensive information that includes the literatures on its reference product.

General Principles – Comparative Clinical Study (2)

Clinical data package

Case 1

PK study

Clinical efficacy Study
(including evaluation of safety)

Case 2

PK study + PD study (or PK/PD study)

A clinical study to evaluate safety

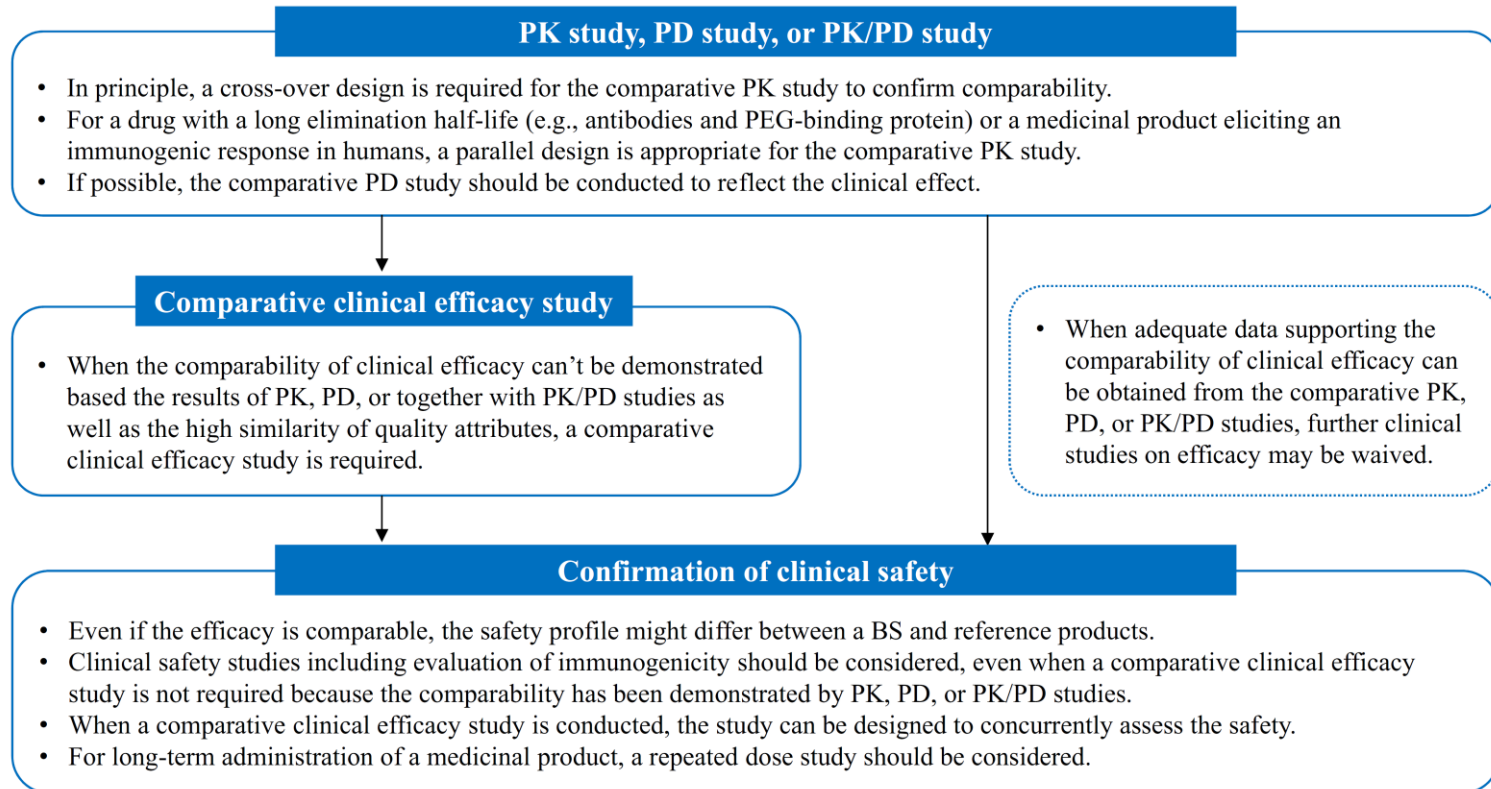
- Clinical PK and PD studies

- ✓ A Comparative PK study is necessary to confirm the potential differences between both products.
- ✓ If possible, select a PD marker that reflects the clinical effect of the product and perform a comparison using the PD as an index.

- Comparison of clinical efficacy

- ✓ When adequate data supporting the comparability of clinical efficacy can be obtained from the comparative PK, PD, or PK/PD studies, further clinical studies on efficacy may be waived.

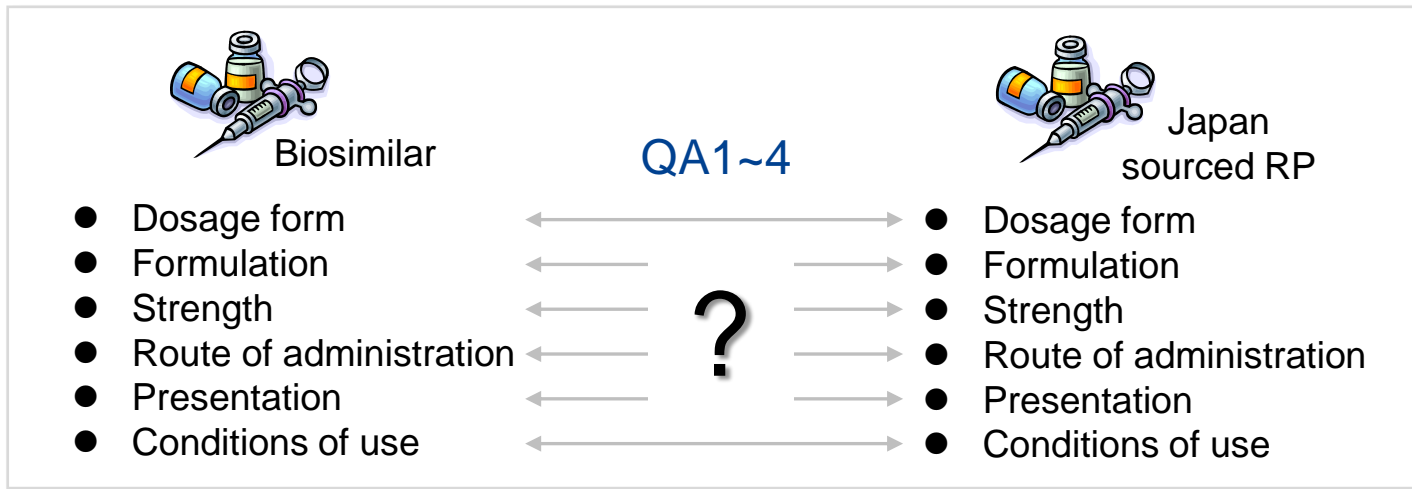
Overview of Comparative Clinical Studies for Biosimilar Development



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Frequently Asked Questions



QA5



non-Japan sourced RP

QA6 : Post-approval manufacturing change

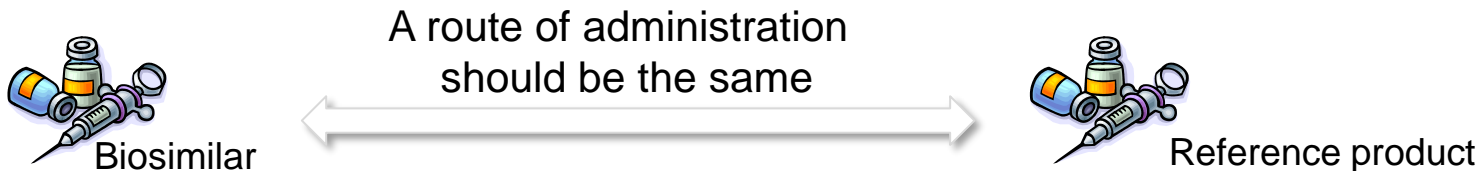
QA7 : Extrapolation

QA8 : Interchangeability

(QA1) Can a proposed biosimilar product have a dosage form, a formulation, or a strength that is different from its reference product?

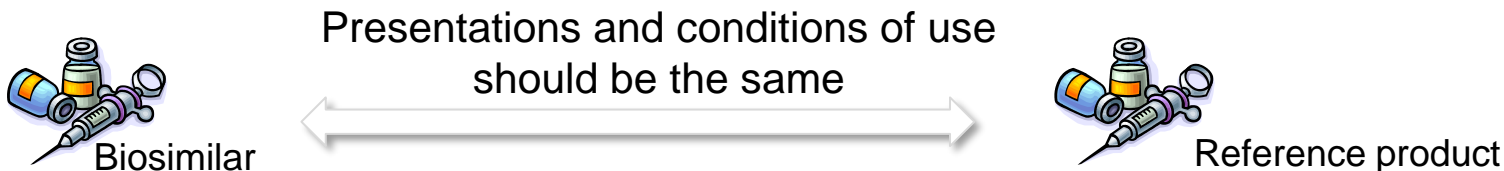
- Differences in a dosage form, a formulation, and a strength : **Acceptable if justified.**
 - A dosage form
 - ✓ A different dosage form than its reference product may be acceptable in a certain justified case. For example, it may be acceptable that the biosimilar uses a liquid form, while its reference product uses a lyophilized form.
 - A formulation
 - ✓ It is not necessary for the formulation of the biosimilar to be the same as that of its reference product, as long as there are no adverse effects on efficacy and safety.
 - A strength
 - ✓ If it is possible to administer the same amount of the active ingredient using the dosage and dose regimen of its reference product, the same active ingredient concentration is not essential.

(QA2) Can a proposed biosimilar product have a route of administration that is different from its reference product?



- Differences in a route of administration : **Not acceptable**
 - a route of administration
 - ✓ The administration route of a biosimilar should be the same as that of its reference product.

(QA3) Can an sponsor obtain approval of a proposed biosimilar product for fewer than all presentations, or fewer than all conditions of use for which its reference product is approved?



- Fewer than all presentations : **Not acceptable**
 - Generally, it is necessary to obtain approval of all presentations which its reference product has been approved.
- Fewer than all conditions of use : **Not acceptable**
 - Generally, it is necessary to obtain approval for all indications, dosages, and administrations for which the re-examination period and patent period has expired for its reference product.

Primer on Biosimilar-Related Regulatory Topics for Regulatory Reviewers (IPRP/Jan,9,2022)

(QA4) May a sponsor seek approval for a condition of use that has not previously been approved for its reference product?



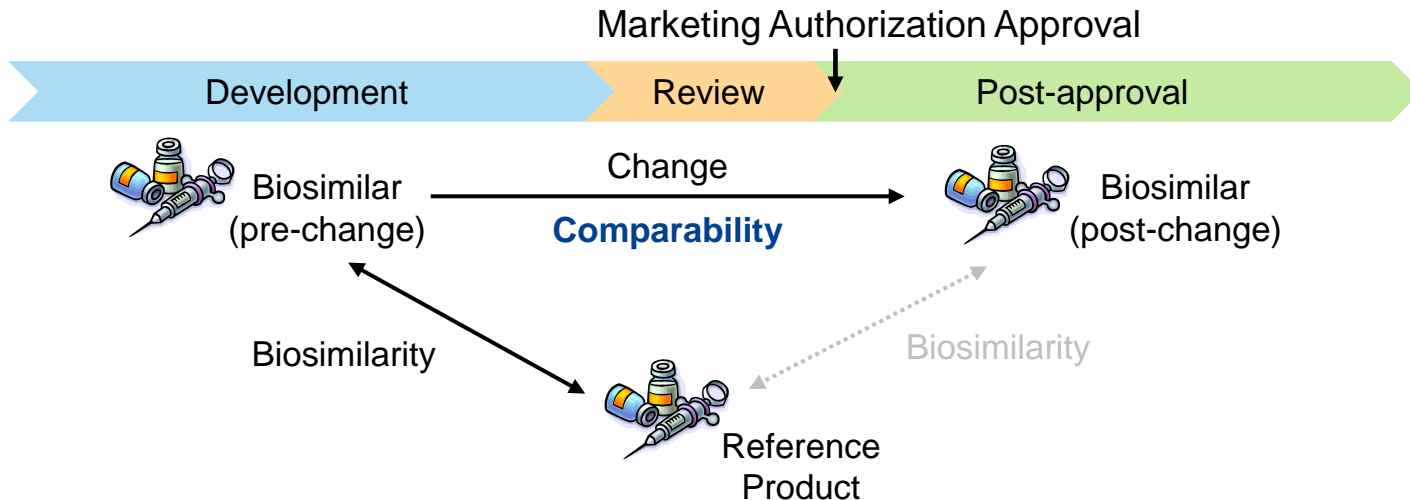
- A different conditions or indications of use : **Not acceptable as a biosimilar**
 - ✓ If the product is developed as a biosimilar product, conditions of use are limited to those of its reference product. A sponsor of biosimilar products can obtain approval for conditions of use that have not previously been approved for its reference product if the sponsor conducts adequate clinical studies, but the submission would not be reviewed as biosimilar.

(QA5) Can a sponsor use non-Japan sourced reference product in comparability exercise?



- Non-Japan sourced reference product : **It's acceptable**, but a sponsor should confirm the comparability to its reference product which is approved in Japan.
 - When clinical trials using a drug product approved overseas as its reference product are used for biosimilar applications in Japan, it should be justified that the domestically approved product and the overseas approved product be regarded as identical based on the results of comparative analytical studies of both.

(QA6) What is the nature and type of information that a sponsor should provide to support a post-approval manufacturing change for a licensed biosimilar product?



- A sponsor should perform comparability studies to demonstrate the comparability between pre-change and post-change biosimilar products in accordance with ICH Q5E guideline.
- On the other hand, it is not necessary to perform re-demonstration of biosimilarity.

Primer on Biosimilar-Related Regulatory Topics for Regulatory Reviewers (IPRP/Jan 9,2022)

(QA7) Is it possible to obtain the indications not directly studied?

- Extrapolation of the indications not directly studied : **Acceptable**
 - In the case where efficacy and safety profile of the biosimilar have been demonstrated to be comparable to that of its reference product in one of the latter's indications, if comparability of pharmacological effects can be expected and the sponsor can explain that there are no differences in safety profile in the other indications, it may be possible to extrapolate those indications to the biosimilar.
 - However, where each relevant indication has a different mechanism of action or the mechanism of each indication remains unclear, the comparability of efficacy with the reference product should be demonstrated for each indication, without extrapolation.

Primer on Biosimilar-Related Regulatory Topics for Regulatory Reviewers (IPRP/Jan,9,2022)

(QA8) What is meant by the term “interchangeable” and are there different expectations/clinical implications compared to the term “biosimilar”?

- Japanese regulations do not give a definition of “interchangeable” for biosimilar products.
- The naming system does not allow for substitution for biosimilar at pharmacy level.
- The switching to biosimilar products depends on the health care professional’s decision, without regulatory restriction.

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Re-evaluation of the Necessity of a Comparative Efficacy Study in the Development of Biosimilars (1)

The Path towards a Tailored Clinical Biosimilars Development
(Martin Schiestl, *et al. BioDrugs*, 2020, 34, 297-306.)

- This study was reported by members of the following pharmaceutical companies.
Sandoz GmbH, Mylan Pharm. Private Ltd., Celltrion Inc., Samsung Bioepis Co. Ltd.,
Polpharma Biologics S.A., Formycon AG, bioeq GmbH, Teva Pharm. Ind. Ltd., IGBA, Geneva
- In this paper, the authors are discussing the necessity of a comparative efficacy study in the development of biosimilars.
- This study is based on a review of the EU and/or the US approved public information on biosimilars up to November 2019.

Re-evaluation of the Necessity of a Comparative Efficacy Study in the Development of Biosimilars (2)

Abstract

Since the first approval of a biosimilar medicinal product in 2006, scientific understanding of the features and development of biosimilar medicines has accumulated. This review scrutinizes public information on development programs and the contribution of the clinical studies for biosimilar approval in the European Union (EU) and/or the United States (US) until November 2019. The retrospective evaluation of the programs that eventually obtained marketing authorization and/or licensure revealed that in 95% (36 out of 38) of all programs, the comparative clinical efficacy studies confirmed similarity. In the remaining 5% (2 out of 38), despite meeting efficacy outcomes, the biosimilar candidates exhibited clinical differences in immunogenicity that required changes to the manufacturing process and additional clinical studies to enable biosimilar approval. Both instances of clinical differences in immunogenicity occurred prior to 2010, and the recurrence of these cases is unlikely today due to state-of-the-art assays and improved control of process-related impurities. Biosimilar candidates that were neither approved in the EU nor in the US were not approved due to reasons other than clinical confirmation of efficacy.

This review of the development history of biosimilars allows the proposal of a more efficient and expedited biosimilar development without the routine need for comparative clinical efficacy and/or pharmacodynamic studies and without any compromise in quality, safety, or efficacy. This proposal is scientifically valid, consistent with regulation of all biologics, and maintains robust regulatory standards in the assessment of biosimilar candidates.

Note: The findings and conclusion of this paper are limited to biosimilar products developed against the regulatory standards in the EU and the US.

(Martin Schiestl, *et al. BioDrugs*, 2020, 34, 297-306.)

Re-evaluation of the Necessity of a Comparative Efficacy Study in the Development of Biosimilars (3)

MHRA (*Guidance on the licensing of biosimilar products / July 7, 2022.*)

Confirmatory efficacy trial

Although each biosimilar development needs to be evaluated on a case by case basis, it is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach. Therefore, a well-argued justification for the absence of an efficacy trial should be appended to CTD Module 1 of the submitted application.

Applicants are encouraged to seek scientific advice to discuss this approach as soon as they have sufficient comparative analytical and functional data to support it. However final acceptance of this approach would only be considered after submission of the complete data package. The general principles to be used in this justification are summarized hereafter.

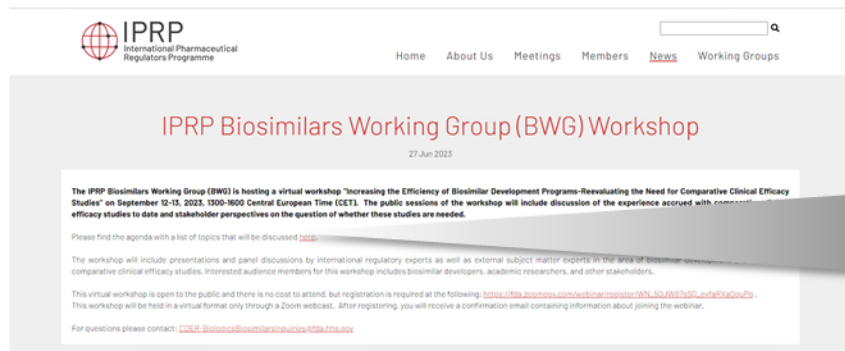
Re-evaluation of the Necessity of a Comparative Efficacy Study in the Development of Biosimilars (4)

WHO (*Guidelines on evaluation of biosimilars* (WHO Technical Report Series, No.1043, 2022.))

A comparative bioequivalence study involving PK and/or PD comparability is generally required for clinical evaluation. An adequately powered 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 need for a comparative clinical efficacy and safety trial for the proposed biosimilar (and type of trial if required) will be influenced by factors such as:

- how well the biosimilar can be characterized;
- the availability of suitable, sensitive and orthogonal assays for adequate analytical and functional characterization;
- the degree of analytical and functional similarity between the biosimilar and RP;
- the existence of a relevant PD parameter;
- the degree of understanding of the mechanism(s) of action of the biological product in different indications and how well these can be investigated in binding and functional *in vitro* tests – the contribution of each mechanism of action to the observed clinical effect is not relevant as long as it can be measured; . . .

Re-evaluation of the Necessity of a Comparative Efficacy Study in the Development of Biosimilars (5)



We will discuss this topic at the IPRP BWG workshop which held in the mid September.

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

Workshop Agenda

Session 1 (Public): <i>Setting the stage—How have we been using comparative clinical efficacy studies (CES) in biosimilar development programs, and what have we learned?</i> Tuesday, September 12, 2023 7:00 am – 10:00 am Eastern Time (US & Canada); 1300 – 1600 Central European Time (CET)	
Welcome/Opening Remarks (10 min)	FDA, United States
Regulatory Experience and Considerations to Date (110 min)	Regulatory Agency Speakers (MHRA, UK; WHO; EMA; Health Canada, Canada; MHLW/PMDA, Japan; MFDS, Republic of Korea; FDA, United States)
Panel, Q&A (50 min)	Moderated by SFDA, Saudi Arabia
Closing Remarks (10 min)	FDA, United States
Session 2 (Public): <i>Stakeholder perspectives on the need for CES in biosimilar development programs</i> Wednesday, September 13, 2023 7:00 am – 10:00 am Eastern Time (US & Canada); 1300 – 1600 Central European Time (CET)	
Welcome Day 2 (5 min)	FDA, United States
Stakeholder Experience with and Perspectives on CES (120 min)	Selected Representative Speakers
Panel, Q&A (45 min)	Moderated by EMA
Closing Remarks (10 min)	EMA
Session 3-5 (Regulators only): <i>Regulatory considerations regarding efficient use of comparative clinical efficacy studies in biosimilar development programs</i> Tuesday-Thursday, September 19-21, 2023 7:00 am-10:00 am Eastern Time (US & Canada); 1300 – 1600 Central European Time (CET)	

Thank you for your kind attention.

HAYAMIZU Kenji, Ph.D
Reviewer

Office of Cellular and Tissue-based products
Pharmaceuticals and Medical Devices Agency (PMDA)

