IPRP
International Pharmaceutical Regulators Programme

6 May 2024

Workshop Summary Report: Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies

IPRP Biosimilars Working Group (BWG)

Contents

1. Introduction

The IPRP Biosimilars Working Group (BWG) aims to facilitate the regulatory process for biosimilar product development. In recent years, increasing calls for streamlining biosimilar development by reducing or eliminating expectations for comparative efficacy studies (CES)[1] have been made, based on the rationale that the clinical study is not a sensitive assay, particularly for the purpose of clarifying differences observed in comparative analytical assessments of a proposed biosimilar and its reference product. Furthermore, if comparative analytics demonstrate a proposed biosimilar is highly similar to its reference product, then differences observed in CES are more likely to be due to clinical study design or conduct variables and on its own should not preclude approval.[2] In response, members of the BWG determined a broader discussion on the basis for and approach to reducing CES expectations was warranted with members of the public and with regulators outside the BWG who were involved with review of biosimilar development programs (BDP). Therefore, in September 2023, the IPRP BWG hosted a virtual workshop, "Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies." Global regulators and industry subject matter experts convened to present on the topic of biosimilar development and CES for an audience of interested stakeholders (e.g., sponsors, academic researchers). Furthermore, the workshop provided a platform for participants to discuss innovative strategies for enhancing the efficiency of biosimilar development, ultimately enhancing patient access to these vital biological medications. One of the first events to convene both global regulators and public speakers on the topic, the five-day workshop was structured to maximize engagement and involvement of participants.[3] The first two sessions, which were open to the public, provided an opportunity for dialogue on streamlined expectations regarding the use of CES. Through this approach, IPRP BWG aimed to incorporate public perspectives and promote transparency in shaping regulatory guidelines. The subsequent three sessions were limited to regulators to maximize opportunity for open and interactive discussions regarding regulatory considerations to streamline BDP, specifically focused on CES.

The IPRP BWG sought nominations for workshop speakers and panelists through internal (e.g., BWG members) and external (e.g., Association for Affordable Medicines, Biosimilars Forum, International Generic Biosimilars Medicines Association) engagements. Speakers for the public sessions were selected by global stakeholders based on the capability to articulate industry viewpoints and educate public attendees about CES requirements. Speakers for the regulator's sessions were selected based on experience reviewing CES data.[4]

This report provides a summary of both the public and regulators sessions of the five-day workshop, highlighting key themes and discussion topics.[5] In addition, conclusions and next steps for regulators are highlighted, emphasizing the importance of this workshop in promoting growth and adaption of the global regulatory landscape for biosimilars.

---

[1] Terminology note: In this document, the term "comparative efficacy study (ies)", abbreviated "CES," is used to describe clinical studies in a patient population comparing a biosimilar and its reference biologic for effects on a primary endpoint related to efficacy. These studies were referred to as "Comparative Clinical Efficacy Studies" in the title of the IPRP September 2023 workshop.

[2] Bielsky MC et al. "Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial" Drug Discov Today (20 20); 25: 1910-1918. Doi: 10.1016/j.drudis.2020.09.006.

[3] Event Agenda

[4] Selection of speakers for the regulator sessions was based purposefully on experience and was not based on scientific views or positions of those considered.

[5] This report is organized by key theme and is not necessarily presented in the order in which discussions took place.

2. Public Sessions

2.1. Background

The goal of the public sessions was to solicit discussion on the need for CES from perspectives of regulators, industry, and academic experts. Public sessions occurred on days 1-2 of the 5-day workshop and were open to the public. Details about each of the public sessions are provided below.

- **Day 1:** Representatives from multiple regulatory agencies presented their experience on the use of CES in BDP and considerations for improving the efficiency of BDP. These presentations were followed by a question-and-answer session, wherein panelists provided multiple perspectives on current requirements, scientific considerations and understanding and other context that comes into play when recommendations regarding the need for a CES are being made.
- **Day 2:** Industry and regulatory stakeholders discussed advantages and disadvantages of including CES in BDP and offered expert opinion on opportunities to streamline biosimilar development.

Section 2.2 provides a summary of discussions held during public sessions.

2.2. Summary of Discussions

2.2.1. Biosimilar Regulatory History and Impact of Comparative Efficacy Studies on Approval

During public sessions, regulatory agency representatives summarized their organizations' regulatory experience with biosimilars, including guidelines and recommendations of their respective agencies. Participants also discussed the role of CES in biosimilar development and their impact on biosimilar approval.

2.2.1.1. Biosimilar Regulatory and Approval History

The regulatory approval of biosimilars historically heavily relied on comparative exercises done across a range of scientific disciplines, including comparative physicochemical, structural and functional data[6], in vitro studies, and clinical studies (PK/PD, safety/immunogenicity, efficacy). Over time, regulatory expectations for BDP have evolved with the advancement in science and technology and accruing regulatory experience with the review of biosimilar applications. Regulators from multiple organizations presented an overview of current statutory requirements and guidelines related to the use of CES in the biosimilar regulatory approvals process, especially in circumstances when robust analytical data were available. For example, the World Health Organization (WHO) Guidelines on Evaluation of Biosimilars were updated in 2022 to indicate that pharmacokinetic (PK)/pharmacodynamic (PD) studies are generally required for clinical evaluation, while CES will typically not be necessary when sufficient evidence of biosimilarity is provided from other components of the biosimilar development program. Table 1 provides a summary of relevant statutes and guidelines for the WHO and six other regulatory organizations represented during the public sessions.[7] Most jurisdictions align with the updated WHO guidelines and do not explicitly require CES, providing flexibility when comparative PK/PD studies are sufficient in demonstrating biosimilarity. Participants stressed that to support justification to waive CES, analytical data must be high quality and robust, with less emphasis on the quantity of data provided.

[6] Terminology note: "comparative physicochemical, structural and functional data" refers to the product quality attributes considered critical in determining whether a biosimilar is "highly similar" to its reference product. This is also known in some jurisdictions as the "comparative analytical assessment" or the "comparative quality assessment." Products must also meet product quality standards for biotechnology products such as those for sterility and stability.

[7] Additional details for the FDA, United States; EMA, Health Canada, Canada; MHLW/PMDA, Japan; and MFDS, Republic of Korea can be found in the IPRP Primer on Biosimilar-Related Regulatory Topics for Regulatory Reviewers.

Table 1: Summary of Statutory Requirements and Guideline Recommendations Regarding Comparative Efficacy Studies

Regulatory Agency	Regulatory Jurisdiction	Relevant Statute	Relevant Guidelines	Summary of Clinical Data Requirements and Recommendations
WHO	Global	N/A	WHO Guidelines on Evaluation of Biosimilars, Section 9.4 Efficacy Studies (Last Updated: April 2022)	Comparative PK/PD and CES should be conducted; a CES may be excluded in cases where PK/PD data provide adequate evidence of biosimilarity and a risk assessment has been conducted to determine if additional safety data are necessary
FDA, United States	United States of America (USA)	Biologics Price Competition and Innovation Act of 2009[8]	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Section D: Clinical Studies - General Considerations (Last Updated: April 2015)	A comparative PK study and either a PD study (if appropriate) or evidence of clinical comparability is required; exceptions may be made in cases that are scientifically justified (e.g., if PK, PD, and immunogenicity profiles indicate no clinically meaningful differences between the biosimilar and the reference product [RP])
European Medicines Agency (EMA)	EU	Directive 2001/83/EC, Annex I, Part II, Article 10(4) and Section 4	Similar Biological Medicinal Products - Scientific Guideline (Last Updated: April 2015)	Evidence of equivalence in PK, equivalence in efficacy, and similarity in safety are required; PD data may serve as evidence of clinical comparability in specific instances
MHRA, UK	United Kingdom (UK)	Human Medicines Regulations, Regulation 53	Guidance on the Licensing of Biosimilar Products, Section 3.3: Clinical (Last Updated: November 2022)	A comparative PK study and a PD study (if appropriate) is required; a CES may not be required in cases that are scientifically justified
Health Canada, Canada	Canada	Food and Drugs Regulations, Part C, Division 8	Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs (Last Updated: August 2022)	A comparative PK and/or PD study is generally expected; a CES is expected in most cases, except when other data (e.g., a PD endpoint) provides sufficient evidence of clinical comparability

[8] The BPCI Act of 2009 amended Section 351 of the Public Health Service (PHS) Act.

Regulatory Agency	Regulatory Jurisdiction	Relevant Statute	Relevant Guidelines	Summary of Clinical Data Requirements and Recommendations
MHLW/PMDA, Japan	Japan	Pharmaceuticals and Medical Devices Act	Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilar, Section 6: Clinical Trials (Last Updated: February 2020)	A comparative PK study and a PD study (if appropriate) is expected; a CES is expected except in the case where PK and/or PD data provide sufficient evidence of clinical comparability
MFDS, Republic of Korea	Republic of Korea	Pharmaceutical Affairs Act (PAA)	Guideline on Evaluation of Biosimilar Products, Section 7.4: Efficacy Study (Last Updated: July 2022)	Comparative PK and PD studies are required; and a CES may be not necessary if comparability can be demonstrated based on confirmatory PD study

Since the establishment of guidelines for biosimilars, regulators have gained valuable experience with the challenges and circumstances that arise in biosimilar development and review. This includes rigorous consideration of the factors that influence the need for CES to demonstrate biosimilarity to a reference product (RP). Regulators from multiple organizations presented data summarizing their regulatory approval history of biosimilars and the role of CES in determinations for approval. Table 2 provides a summary of regulatory approval history as presented by these regulatory agencies during the public sessions.

*Table 2: Regulatory Approval History of Biosimilars and the Role of Comparative Efficacy Studies**

Regulatory Agency	Regulatory Jurisdiction	Total # Biosimilars Approved	# Biosimilars Approved with a CES	# Biosimilars Approved Without a CES
WHO	Global	N/A	N/A	N/A
FDA, United States	United States of America (USA)	42	**	**
EMA	EU	86	**	**
MHRA, UK	United Kingdom (UK)	**	**	**
Health Canada, Canada	Canada	53	44	9
MHLW/PMDA, Japan	Japan	32	24	8
MFDS, Republic of Korea	Republic of Korea	23	22***	1

*Data presented/available at the time of workshop dated 9/12/23; not reflective of updated approvals

**Regulatory history not presented.

***CES data in 2 biosimilars are supportive and are not determinant for approval.

2.2.1.2. *Impact of Comparative Efficacy Studies on Biosimilar Approval*

Regulatory stakeholders also presented and discussed perspectives regarding the impact of CES data on decisions for biosimilar product approval. One recent review was highlighted, wherein a retrospective review of biosimilars approved in the EU and US from 2006 – 2019 concluded that performance of a successful CES (i.e., biosimilar and reference products have comparable efficacy) is not directly correlated to biosimilar approval.[9] These results suggest that the information provided by CES are often not determinant regarding approval of a biosimilar product. A complementary review paper that examined whether failed CES led to the disapproval of biosimilar candidates was also presented.[10] Ultimately, in cases where the CES data were not successful but where the products were approved anyway, approval was based on (1) highly similar physicochemical, structural and functional data and (2) PK profile comparability, supporting the idea that the physicochemical, structural and functional characterization of the biosimilar candidate is most critical for its approval. The authors of this review concluded that the comparative quality studies and standalone quality data is predictive for the marketing authorization of a biosimilar candidate and that regulatory guidelines should be revised appropriately.

Participants also discussed whether clinical confirmation of comparable efficacy could be replaced by comparative functional characterization data (comparative in vitro data) to streamline biosimilar development and approval. These data include structural and functional assessments of similarity in addition to results from precise binding assays to confirm comparable target and receptor binding activity using suitable in vitro bioassays. Multiple stakeholders expressed that successful functional characterization using in vitro bioassays may preclude the need for a CES, in part due to the high specificity and sensitivity of these functional characterization assays for detecting clinically meaningful differences. If a CES is to be used, it should be designed purposefully to answer a specific question that cannot be addressed from the comparative functional characterization.

Key points of discussion addressed the utility of PK data and the importance of these data for resolving uncertainty in biosimilar applications. On this topic, a review paper was presented which examined whether biosimilarity could be based solely on comparative physicochemical, structural and functional data and PK data in 33 biosimilar applications submitted to the EMA.[9] In these applications, residual uncertainties were primarily resolved by evaluation of comparative quality and PK data. The authors concluded that an assessment of biosimilarity could be based on comparative quality and PK data alone, whereas comparative efficacy data were less impactful. Participants further discussed what uncertainty in quality differences was being addressed by PK studies; specifically, those differences between the biosimilar and its RP that are likely to impact on systemic exposure of the biosimilar, which, in turn, could impact product efficacy. Discussants further noted that PK studies can often be performed in healthy subjects and designed with lower sample sizes compared to CES. Additionally, these studies should provide information on safety, tolerability, and immunogenicity of the product. Participants added that safety and tolerability can be more rigorously (e.g., using blinding protocols) and frequently assessed in PK studies than in clinical efficacy studies. When PK studies are not feasible or relevant (e.g., ocular products administered via intravitreal injection), additional discussion may be required to determine whether physicochemical, structural and functional characterization studies are sufficient or if other studies, including CES, are necessary to establish comparable efficacy and safety. The topic of PK similarity studies was also discussed during the regulator's sessions, and some of the other challenges with these studies are expanded on further in Section 3.2.4.1.

2.2.2. Utility and Limitations of Comparative Efficacy Studies

Building on the perspectives and regulatory history examined in Section 2.2.1, participants also discussed the utility and limitations of CES in the demonstration of biosimilarity.

---

[9] Schiestl M et al. "The path towards a tailored clinical biosimilar development." BioDrugs (2020); 34:297-306. DOI: 10.1007/s40259-020-00422-1

[10] Kirsch-Stefan N et al. "Do the outcomes of clinical efficacy trials matter in regulatory decision-making for biosimilars?" BioDrugs (2023); 37:855-871. DOI: 10.1007/s40259-023-00631-4. This publication was in press at the time its results were discussed during the workshop.

2.2.2.1. *Utility of Comparative Efficacy Studies*

Participants noted that while CES may not contribute to the establishment of biosimilarity, these studies may provide reassurance to providers, patients, and regulators. Specifically, stakeholders suggested that medical professionals and patient groups feel more comfortable when comparative efficacy data are provided, especially when patients are switching from a reference product to a biosimilar; however, participants emphasized that CES take a substantial amount of time and may still be underpowered. Participants considered whether reducing requirements for CES duration or sample size (i.e., number of patients) would result in inadequate data to inform approval decisions. Further, it was suggested that the absence of CES data may decrease prescriber confidence and result in decreased uptake and utilization of biosimilar medications. Participants emphasized the importance of educating prescribers about cases where CES may not be necessary. The topic of educating stakeholders was also discussed during the regulator's sessions, and education efforts are expanded on further in Section 3.2.1. As a potential solution, participants suggested that a small clinical study with descriptive analysis of patient outcomes could provide a similar level of comfort to providers and patients in lieu of CES. With this possibility could be additional considerations, such as concern around enrolling patients in such trials when there is no promise of obtaining meaningful data and chance findings arising from studies which may result in need for additional data. Stakeholders emphasized that the regulatory impact of such studies should be carefully weighed.

2.2.2.2. *Limitations of Comparative Efficacy Studies*

Regarding the limitations of CES, participants discussed that these studies may not be suitable to address residual uncertainties that remain after evaluation of comparative quality studies (physicochemical, structural and functional data). Specifically, CES typically lack the sensitivity needed to detect differences between a biosimilar and RP compared to comparative PK in healthy volunteers, to strengthen the totality of evidence, or substantiate evidence of comparability between the two products. Participants suggested that CES should not be required when a product is well-characterized in terms of its mechanism of action (MOA), target binding, and function. One stakeholder introduced a review which examined how CES contributed to the assessment of biosimilar applications, focusing on complex molecules without a PD biomarker.[11] Across all cases evaluated within this study, CES failed to provide any critical information for establishing biosimilarity; the authors concluded that CES are insufficient to (1) resolve residual uncertainties or (2) "rescue" the approvability of a product application with insufficient or weak quality data. As such, the authors suggest that CES are an inefficient use of resources when aiming to establish biosimilarity. Participants acknowledged that CES are currently being used in practice to address residual uncertainty arising from the comparative quality assessment but noted that the uncertainty in question is often trivial and the outcome rarely exerts strong influence on regulatory decision making. If residual uncertainty remains following the comparative quality assessment, participants suggested that additional comparative physicochemical, structural and functional testing is the most appropriate solution. While sponsors have asked regulatory agencies for guidance around quantifying uncertainty, participants noted that residual uncertainty is difficult to quantify and needs to be addressed on a case-by-case basis. While not the focus of this discussion, workshop stakeholders also suggested a shift away from term "residual uncertainty," and suggested that regulators emphasize the scientific questions that remain around biosimilarity.

2.2.3. Biosimilar Development Challenges

Industry stakeholders and regulators identified several challenges of biosimilar development. Regulators emphasized challenges related to the timing of biosimilar development and providing evidence of comparative immunogenicity, whereas industry representatives noted the lack of harmonized requirements among different regulatory agencies and challenges of manufacturing scale-up for biosimilar products.

2.2.3.1. *Timing Challenges of the Stepwise Approach*

Participants indicated that regulators are encouraging developers to share data and engage with them early in the biosimilar development process. Historically, many regulators recommended the use of a stepwise approach in BDP, wherein sponsors

[11] Bielsky MC et al. "Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial" Drug Discov Today (2020); 25: 1910-1918. Doi: 10.1016/j.drudis.2020.09.006.

first conduct detailed analytical characterization studies followed by tailored comparative exercises in parallel. Participants argued that this stepwise approach assumes the design and implementation of a clinical study(ies) occurs after a robust comparative quality package is completed, and therefore introduces a costly mismatch against the practical aspects of a BDP. Industry stakeholders suggested that to move away from a "stepwise approach" to a combined "stepwise and tailored approach", regulators would need to define success at the level of the quality program so biosimilar product developers can focus on measurement of critical quality attributes (QAs). This would require closer collaboration between developers and regulators to ensure a quality program is relevant to the establishment of biosimilarity. This collaboration may allow for CES to be waived more routinely if developers provide robust comparative physicochemical, structural and functional data early in the BDP.

2.2.3.2. Quality Data Limitations

Another regulatory challenge identified is limitations in the predictive value of comparative quality data for immunogenicity and associated clinical outcomes. While immunogenicity of a reference product (RP) is well known, it is important that developers provide assurance that minor analytical differences between a biosimilar and RP do not result in immunogenicity differences. Participants emphasized that factors potentially impacting on immunogenicity should be identified and addressed in the comparative quality studies and standalone quality data, noting that information on immunogenicity rates in the clinical study stages is not likely to be interpretable out of context. In response to a question regarding use of postmarketing data to streamline BDPs, stakeholders discussed the importance of having what is needed to demonstrate biosimilarity at the time of approval, rather than retroactively (e.g., using postmarket surveillance data). Both regulators and industry stakeholders agreed that the latter is not viable, and that utility of postmarketing data would depend on context, e.g., if relevant postmarketing data from one region were available to support a marketing application in another region. Participants did not see a role for taking the approach of conditionally approving a biosimilar product with postmarketing clinical requirements, as a proposed biosimilar would have to be able to meet expectations for approval at the time of an approval decision.

2.2.3.3. Other Challenges Expressed by Industry Stakeholders

Industry stakeholders raised multiple points regarding challenges for BDP. For example, in some jurisdictions, biosimilars are expected to be compared to the locally approved RP and not a foreign version of the RP. When use of a foreign RP is allowed, it may require scientific bridging data between the foreign and local versions of the RP. Therefore, potential approaches that would enable a more straightforward use of a global RP as a comparator product are of interest, namely as one potential mechanism to improve cost effectiveness, accessibility, and availability of data of value for biosimilar developers and regulatory agencies. In addition, participants suggested the option of a timely parallel scientific advice pathway, wherein developers could propose details of their BDP to both EMA and FDA, United States and receive feedback from each in a collaborative and timely manner. Another unaddressed challenge raised by industry stakeholders is the lack of harmonized regulatory guidelines regarding biosimilar candidates that demonstrate enhanced pharmacological characteristics (e.g., improved safety and efficacy compared to the RP). Regulators acknowledged that different regulatory agencies have different legal frameworks for assessing such products. As a result, these products may be treated as standalone biologics, new drug submissions, or biosimilars depending on the jurisdiction where the application is submitted. Industry stakeholders also raised the limitations of pharmacodynamic (PD) biomarkers, specifically in their dose sensitivity and/or high baseline "noise;" which to some stakeholders meant that PD biomarkers, particularly ones not yet widely accepted, would not be a feasible expectation to replace reliance on comparative efficacy data. These stakeholders emphasized that development programs relying on a robust comparative analytical data package which includes a comprehensive panel of precise functional assays and a comparative clinical pharmacokinetic study should be able to justify foregoing additional expectations of comparative efficacy or PD.

3. Regulators Sessions

3.1. Background

The overarching goal of the regulators sessions was to provide an open platform for discussions regarding regulatory considerations to streamline BDP. Specifically, regulators considered the circumstances in which a CES may or may not be needed for the demonstration of biosimilarity. Participants also discussed a potential risk-based framework for evaluating when CES would be needed. Details about each day of the regulator's sessions, which occurred on days 3-5 of the 5-day workshop, are provided below:

- **Day 3:** Participants discussed the results of a survey conducted prior to the workshop to assess the current perspectives of global regulators about CES. Following presentation of the survey results, regulators shared their insights and experiences regarding the role of CES for resolving uncertainty in evaluations of biosimilar products.
- **Day 4:** A subject matter expert in biotechnology product quality, manufacturing, and controls provided contextual information on the comparative analytical assessment and analytical assessment capabilities. Participants discussed a potential risk-based framework for regulatory decision making regarding the need for CES. Regulators discussed when the need for a CES can be justified based on specific risks or circumstances related to uncertainties, product factors, or clinical factors.
- **Day 5:** Regulators continued discussions on topics covered during the previous two days. In addition, a brief poll was conducted to assess participants' perspectives on whether there is flexibility to move away from default expectations for CES. The regulators sessions concluded with a brief discussion on potential future deliverables regarding the outcomes of this workshop.

Section 3.2 provides a summary of discussions held during regulators sessions.[5]

3.2. Summary of Discussions

3.2.1. Stakeholder Education Regarding Comparative Efficacy Studies

In a survey of global regulators conducted prior to the workshop, a significant number of responses suggested that regulators believed a CES is required by law or guidance for approval of a biosimilar.[12] However, discussions during the regulators sessions clarified that legislation does not mandate a CES for biosimilar approval in most jurisdictions, and guidances are not legally binding, giving regulators flexibility to determine the need for a CES on a scientific basis. Regulators acknowledged there are misconceptions or confusion, even within regulatory agencies, about whether a CES is required as a legal or scientific matter. Regulators discussed various educational efforts needed to improve global awareness of the biosimilar approval paradigm among regulators, with additional clarity on the role of and flexibility available regarding CES data for biosimilar approval.

3.2.1.1. Educating Regulatory Stakeholders

Regulators strongly concurred with the necessity of internal communication efforts between quality and clinical data review experts within regulatory agencies on topics related to analytical assessment of biosimilar candidates. For example, regulatory stakeholders emphasized the need for education to provide clinical reviewers with an overview of the entire quality assessment process and structural, functional, and clinical relationships. Participants agreed this would help to minimize uncertainties about the safety and efficacy of biosimilar candidates following from the comparative quality

[12] The IPRP BWG solicited feedback from regulators at international regulatory agencies to ascertain perspectives on whether a CES is deemed necessary for biosimilar approval in compliance with legal mandates or as recommended by established guidelines. Regulatory agencies submitted the feedback as either a single collated agency response or as individual responses of participants within the agency. While results cannot be accurately quantified due to this methodology, discussants suggested the survey was thought to be a fair representation of regulator perspective.

assessment. Emphasis should be placed on the relationship between structural and functional data including mechanism of action (MOA) of the reference product (RP) to help reviewers assess the impact of differences observed in comparative quality attributes on the clinical performance of the proposed biosimilar and its RP. In addition, the statistical approaches frequently used for analysis of comparative quality data diverge from those commonly used for evaluating clinical data, thus necessitating clarification for interpretation by non-quality experts. Most importantly, regulators urged that educational efforts clarify that if comparative quality and PK data convincingly demonstrate biosimilarity, data from a CES does not substantially contribute to the demonstration of biosimilarity. On the other hand, if there are differences between the biosimilar and RP in terms of quality and/or PK data, clarity on the potential impact of such differences is most likely to be obtained through generation and review of additional quality and/or PK data because CES lack the sensitivity to assess the impact of small differences in critical quality attributes (CQA) and PK parameters. Regulators emphasized that if the quality and analytical package is not sufficiently robust, comparative clinical data (e.g., from a CES study) would not rescue the product data package toward approval.

3.2.1.2. Educating Healthcare Professionals

Regulators agreed that external education efforts are also needed to increase awareness among healthcare professionals. These efforts should highlight the rigor and transparency of analytical studies that convincingly predict comparable safety and efficacy of biosimilars to the RP. With improved understanding of these analytical studies and their conclusions, healthcare providers may be more accepting of biosimilars without relying on data from CES, potentially reducing the duration and cost of BDPs.

3.2.2. Highlighted Presentation: Product Quality Assessment

The regulators sessions included a presentation focused on the comparative product quality assessment in the overall demonstration of biosimilarity. The presentation addressed whether critical prerequisites for demonstration of biosimilarity are convincingly met by comparative physicochemical, structural, functional, and PK parameters.[13] To this end, the presentation included an overview of the considerations for demonstrating biosimilarity from the quality perspective and highlighted key takeaways from recent studies that evaluated quality and immunogenicity data for biosimilars approved in the EU. The following sections provide a summary of the information in the presentation.

3.2.2.1. Process of Demonstrating Biosimilarity

The demonstration of biosimilarity requires a reverse development process that typically begins with identification and risk assessment to define the critical quality attributes (CQAs) for the proposed RP using various risk assessment tools according to the ICH Q9. Publicly available knowledge about the RP (e.g., MOA) serves as the cornerstone for this identification and criticality assessment; CQAs are selected based on the known or uncertain impact of each attribute on the potency (i.e., efficacy), PK, or immunogenicity of the biosimilar. Biosimilar developers must then conduct detailed characterization to gain a complete understanding of the RP, including batch-to-batch variability. Based on this extensive characterization, a quality target product profile (QTPP) of the proposed biosimilar is established. The QTPP is a prospective summary of the ideal quality characteristics of a drug product. The manufacturing process must be designed to consistently produce the proposed biosimilar according to the QTPP.

The most critical step of biosimilar development is the completion of comparative physicochemical, structural and functional studies to demonstrate that the proposed biosimilar is highly similar to RP in terms of CQAs (e.g., primary and higher-order structure, post-translational modifications, biological activity). It is of particular importance that the methods used for characterization studies should be sound, state-of-the-art, and of appropriate sensitivity and specificity. In addition, orthogonal methods should be used for CQAs, if possible. The goal of comparative quality studies is to be as comprehensive

[13] The critical prerequisites for demonstration of biosimilarity include: (1) The amino acid sequence, dosing, and route of administration must be identical to the RP, (2) the active substance must be highly similar to the RP in terms of molecular and biological characteristics, (3) minor differences in quality attributes (QAs), strength, pharmaceutical form, and formulation excipients may be accepted but must be justified, (4) significant differences in the quality profile of the active substance and clinically significant differences in PK, efficacy, or safety profile, including immunogenicity are not allowed.

as possible to minimize the possibility of undetected differences between biosimilar and RP that could impact safety and clinical performance of the proposed biosimilar. The presenter underscored that comparative functional testing related to MOA of the RP – and by definition the biosimilar – is of most importance to provide strong evidence of biosimilarity between the two products. Furthermore, because the safety profile of a biological product depends on its biological function, comparative functional testing provides assurance of similarity between the biosimilar and RP safety profiles.

The assessment of physicochemical, structural and functional similarity at an analytical and in vitro level is also referred to as the "comparative analytical assessment" in some jurisdictions. Of note, this analytical similarity assessment largely follows the basic principles outlined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5E guideline for comparability assessment of manufacturing process changes. The proposed biosimilar and the RP need not be identical but highly similar, and any differences in quality attributes (QAs) should be sufficiently justified to minimize the risk of impacting the safety or efficacy of the product. The most common approach for similarity assessment requires a demonstration that all batches of the biosimilar exhibit QAs within the similarity ranges determined from the RP characterization, that account for (1) within-batch and between-batch variability of the RP and (2) the respective criticality of QAs evaluated. Regulators emphasized the need to continue discussions on appropriate statistical approaches for analytical similarity assessment, especially amid growing interest in relying less on clinical data in near future.

The presentation concluded with a highlight of key findings from recent studies that reviewed and evaluated quality and immunogenicity data of biosimilar monoclonal antibodies (mAbs) and fusion proteins approved in the EU.[14,15,16] These studies collectively suggest that knowledge of the RP is the best source of data to predict immunogenicity of a biosimilar, challenging a prevalent notion that immunogenicity is the primary and unpredictable risk of biosimilar development. Furthermore, these studies demonstrate that a comprehensive and robust comparative quality data package is the most critical aspect of the comparability exercise for biosimilar approvals. Taken together, these studies challenge the usefulness of efficacy, safety, and immunogenicity data from CES and suggest a tailored approach to comparative clinical data requirements based on the additional evidence provided.

Table 3. Product Quality Literature Review Highlights

- Comprehensive characterization of biosimilars using state-of-the-art and highly sensitive analytical methods together with PK data often provide sufficient information for demonstration of biosimilarity.
- Biosimilars show similar safety and intrinsic immunogenicity (i.e., anti-drug antibody responses) profiles compared to RPs; therefore, knowledge of the RP is the most valuable predictor of biosimilar immunogenicity.
- In the cases evaluated, CES data supported the demonstration of biosimilarity using quality and analytical data, but in no instances were these data used to resolve quality concerns.
- Analytical and functional data were predictive for the marketing authorization of biosimilar candidates, irrespective CES outcome.

Following the presentation, discussions were focused on the utility of CES in resolving quality data concerns (see Sections 2.2.2.1 and 0), use of the term "residual uncertainty" (see Section 2.2.2.2), applicability of findings of the review studies to less characterized products (see Section **Error! Reference source not found.**), and the need for educating clinical reviewers/experts about analytical assessment approaches and interpretation (see Section 3.2.1.1). In addition, regulators discussed the value of predictive models in establishing correlations between QAs and clinical outcomes. They agreed that predictive data models are incredibly powerful but require an immense amount of data for validation, and therefore, are unlikely to be useful to consistently and accurately and precisely predict the impact of QAs on clinical outcomes. Regulators also discussed

[14] Kurki P et al. "Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective." Drugs (2021); (16):1881-1896. DOI: 10.1007/s40265-021-01601-2

[15] Guillen E et al. "A data driven approach to support tailored clinical programs for biosimilar monoclonal antibodies." Clin Ph armacol Ther (2023); 113:108-123. Doi: 10.1002/cpt.2785

[16] Kirsch-Stefan N et al. "Do the outcomes of clinical efficacy trials matter in regulatory decision-making for biosimilars?" BioDrugs (2023); 37:855-871. DOI: 10.1007/s40259-023-00631-4. This publication was in press at the time its results were discussed during the workshop.

whether statistical approaches to comparative quality data assessment could mitigate the need for CES. Participants generally believed that overemphasizing statistics for analytical assessment may not result in better conclusions, and additionally it is not clear what the best statistical approach would be in the analytical setting, which is quite different than the randomized control trial setting.

3.2.3. Regulatory Considerations Regarding Comparative Efficacy Studies

Regulators also shared their considerations and perspectives regarding CES; key themes included the considerations around the role of CES in resolving uncertainties, lack of understanding of analytical similarity data among stakeholders, and timing challenges of deciding on the need for CES based on a stepwise approach.

3.2.3.1. Considerations Around the Utility of Comparative Efficacy Studies

Regulators' perspectives regarding the utility of CES aligned with conclusions of the two studies previously discussed (see Section 3.2.2). Regulators could not recall any experiences in which a CES led to rejection of a biosimilar application or was used to resolve residual uncertainty that remained after a complete comparative quality and PK assessment. Regulators acknowledged that a CES can only confirm biosimilarity of a proposed biosimilar that is established at the quality and PK level but cannot resolve concerns that remain due to low quality or otherwise insufficient comparative quality or PK data. In participants' experience, uncertainties were resolved by increasing the number of biosimilar lots to better understand batch-to-batch variability, by increasing rigidity in biosimilar development control strategy, or by inclusion of additional comparative quality or PK data. One primary reason that CES cannot resolve uncertainties is because they are not sensitive enough to detect differences between a proposed biosimilar and RP. Some regulators pointed out that CES are often designed for using treatment response rate as the primary endpoint, which may not reflect the complete picture of treatment efficacy. Furthermore, CES may introduce more concerns than they alleviate. For example, CES may produce results that are inconsistent with comparative quality data in supporting biosimilarity, making it challenging to explain the inconsistency. Regulators further acknowledged that the early biosimilar development paradigm included a CES in patients as a final confirmatory step of a stepwise development approach.

3.2.3.2. Lack of Understanding of Analytical Similarity Data

Despite increasing confidence in comparative quality studies including structural and functional data, regulators identified and discussed remaining challenges with relying on physicochemical, structural and functional data as the foundation for BDP and biosimilarity assessment, which may contribute to real or perceived need for CES. Regulators agreed that there are gaps in understanding of the relationships between product QAs and clinical outcomes to predict whether differences in QAs are clinically meaningful. Regulators also suggested that confidence in comparative quality studies for assurance of safety and efficacy can be justified for most cases in which relevant QAs are well understood (e.g., mAbs); however, this does not hold true when the MOA of the RP is unknown. Similarly, regulatory experience with well-characterized biosimilars justifying the sufficiency of analytical data (e.g., mAbs, fusion proteins) may not apply to less characterized products (e.g., naturally derived mixtures, polynucleotides such as defibrotide).

3.2.3.3. Timing Challenges for Waiver of a Comparative Efficacy Study

Another potential challenge is a timing mismatch between when sufficient analytical data have been generated and when regulators can make an informed determination regarding the need for a CES. Regulators often do not have sufficient and mature comparative quality data to determine or advise sponsors on the need for a CES at decision points most critical for early BDP planning. As a result, regulators often opt for a conservative approach due to uncertainties when limited comparative quality data exist. Convergence on a decision-making approach based on the likelihood of analytical differences and the likelihood that those differences may have clinical impact may help resolve this timing mismatch. In addition, guidelines could clarify when a CES is likely to be required depending on data quality and gaps. Of note, some regulators suggested the responsibility is on sponsors to provide sufficient comparative quality data early to enable regulators to make an informed decision on the need for a CES based on a scientific justification.

3.2.4. Clinical Pharmacology Data as an Alternative to Comparative Efficacy Studies

A greater reliance on pharmacokinetic (PK) and pharmacodynamic (PD) similarity studies can potentially streamline BDPs by allowing for shorter and less costly clinical studies that can often be conducted in healthy subjects. Regulators discussed the use of PK and PD similarity data to mitigate the need for CES and identified challenges related to their use.

3.2.4.1. Pharmacokinetic Similarity Data

Regulators agreed that a PK similarity study can be pivotal in demonstrating biosimilarity. A comparative PK study in healthy volunteers is generally more sensitive than a CES in patients, particularly in detecting potential product-related differences between a proposed biosimilar and the RP that can impact systemic exposure. Furthermore, analytical differences are more likely to translate into PK impacts rather than CES endpoints; therefore, a PK study has a higher likelihood of discerning clinically meaningful analytical differences.

Though comparative PK data can be critical for demonstration of biosimilarity and may mitigate the need for a CES, regulators identified and discussed limitations of PK studies and challenges related to their use. Regulators agreed that PK studies may not be relevant for proposed biosimilars that have limited or no systemic exposure (e.g., products administered into the eye). In these situations, regulators acknowledged that there is not current consensus on the circumstances where it may be appropriate to make a regulatory decision based only on comparative quality data (i.e., without PK or efficacy data) or to request a CES. Some regulators questioned whether potential safety concerns arising from minor differences in CQAs of a proposed biosimilar could even be addressed by a CES, since clinical studies are not often statistically powered for safety outcomes. Therefore, the fundamental safety of any biosimilar is known from the safety profile of the RP. A CES of a proposed biosimilar that meets high analytical similarity to an RP would not be powered to demonstrate unique safety concerns.

Other challenges with comparative PK studies relate to generalizability of healthy volunteers to the population of interest (e.g. neonates), and potential vulnerability, feasibility, or data interpretability issues if PK studies need to be done in patients (e.g. orphan indications). Regulators discussed whether differences in PK results could negatively impact regulatory decision making. Some regulators argued that regulatory decision making would depend on the magnitude of differences demonstrated through PK and analytical studies. For example, if comparative quality data are convincing, a small difference in PK results alone may not impact the approval of a proposed biosimilar. Regulators also briefly discussed the situation where a proposed biosimilar exhibits a different PK profile by design compared to the RP and acknowledged a need for future discussions on whether such a product could be approved as a biosimilar.

3.2.4.2. Pharmacodynamic Similarity Data

PD biomarkers are one potential alternative to clinical efficacy endpoints for establishing comparable safety and efficacy of a proposed biosimilar to the RP. Advancing understanding of PD biomarkers may therefore reduce the time and cost associated with BDPs. While regulators discussed the potential use of a PD similarity studies to pre-empt the need for a CES, they also voiced concerns associated with these studies, as also highlighted by industry stakeholders during the public session.

According to a survey of regulators conducted prior to the workshop, most regulators agreed that a PD biomarker could replace the need for a CES if it were validated as a surrogate for product efficacy. Regulators agreed that clinical studies serve to support a demonstration of biosimilarity and not to re-establish efficacy. Some regulators suggested that PD biomarkers may be helpful in resolving uncertainties regarding the functional activity of a proposed biosimilar, even if they were not established as surrogate endpoints; however, few regulators believed that an unvalidated PD biomarker could be used as an alternative to a CES.

During panel discussions in the public sessions, industry stakeholders had voiced some of the challenges and concerns associated with the use of PD biomarkers, and regulators acknowledged these in regulators sessions as well. For example, PD biomarkers are not as sensitive as analytical or PK parameters in detecting potential differences between a proposed biosimilar and the RP. Furthermore, it is challenging to determine a sensitive dose range because a significant change in dose may not alter the PD biomarker response. In addition, reliable PD biomarkers have not been established for many indications, and developing a new PD biomarker requires more effort and resources than may be justified by its impact on

the success of a BDP. Regulators underscored that PD biomarkers may be promising in mitigating the need to conduct a CES in some circumstances, but some of these challenges need to be overcome if they are to be used more widely in BDPs.

3.2.5. Risk-based Framework to Assess the Need for Comparative Efficacy Studies

Regulators discussed a theoretical risk-based framework to identify circumstances where a CES (with efficacy endpoints, not with surrogate endpoints) may be necessary based on scientific justification, rather than default requirement. The discussions were not meant to establish a consensus on the framework but to enable regulators to begin the conversation around a framework for using CES in a more focused way. The framework included three risk factors that may justify the need for a CES: (1) risks related to uncertainties, (2) risks related to immunogenicity, and (3) risks related to clinical factors.

3.2.5.1. Risks Related to Uncertainties

Regulators discussed risk factors related to uncertainties arising from a number of possibilities that may increase the utility of a CES to resolve them. For example, certain products could be extremely complex and/or not well-characterized, such as products that are naturally derived mixtures of proteins. In turn, the MOA and structure-function relationship of the RP and proposed biosimilar may be poorly understood, making it difficult for regulators to rely on comparative analytical data for the demonstration of biosimilarity. Other sources of uncertainty may derive from limited experience with a novel therapeutic protein platform, for example. While many regulators agreed that a CES may be informative based on the uncertainties discussed under this category, some pointed out that its feasibility might also be limited under some special circumstances. For example, feasibility may be an issue if the originator biological product (to be used as a RP for a proposed biosimilar) was only approved for the treatment of a rare disease. Some regulators also noted that it could be difficult to determine whether products that are not yet well-characterized should be considered under the biosimilar approval pathway or pursued as originator biological products.

3.2.5.2. Risks Related to Immunogenicity

Risk factors related to immunogenicity, including product or product class-specific immunogenicity factors, may be another consideration that increases the utility of a CES. Regulators discussed factors that may cause a product to fall into a category of increased concern related to immunogenicity; i.e., ultimately related to the impact of immunogenicity for a given product or product class. For example, if immunogenicity to the RP is known to pose a high or severe clinical risk, if the RP is known to be prone to changes in immunogenicity, or if immune responses to a product may put a non-redundant endogenous counterpart at a risk by cross-reacting with it, resulting into the loss of its physiological function.

3.2.5.3. Risks Related to Clinical Factors

Regulators also discussed clinical factors that may increase the utility of a CES. Specifically, these factors relate to vulnerability of clinical outcomes to perturbation, such as when the RP therapeutic dose range is in the steep part of the dose-range for efficacy and/or safety parameters; and/or other clinical contexts when patient or organ outcomes are particularly vulnerable, which implies any level of uncertainty is intolerable. For example, if the RP is dosed in the steep part of dose-response curve for efficacy or safety parameters, it may be easier for small differences to become clinically meaningful, and therefore a CES may be justified in such cases. However, some noted that this scenario may also make PK and PD similarity studies more informative when combined with a convincing quality data package. Using this information, the outcomes can be linked more clearly with the structure-function relationship of the proposed biosimilar; therefore, regulators may feel more comfortable waiving the need for a CES if the sponsor can provide PD similarity data at two different dosages. Regulators then discussed other clinical contexts that may increase the importance of having clinical data for some stakeholders. For example, if a proposed biosimilar is intended to be used in a vulnerable patient population (e.g., neonates, cancer patients), this reduces tolerance for any degree of uncertainty, which may be ameliorated by a CES. Some regulators suggested that, in addition to products intended to be used in vulnerable patient populations, products locally administered into sensitive organs (e.g., products administered in eye) should be considered under this category. Some regulators believed that the concerns related to vulnerable populations or organs may justify the use of a CES even in the absence of any other types of risks discussed.

Regulators emphasized that these risk factors are not necessarily mutually exclusive, and that a product or product class may concurrently be impacted by multiple risk factors. One benefit of identifying specific risk factors is to also be able to

define a rationale for why most common therapeutic products likely do not need a CES for the demonstration of biosimilarity. Drawing the outlines of where a CES may be helpful allows for their use to be more purposeful and more limited than in current regulatory practice, striking a balance between cost of development and impact on public health.

4. Conclusions and Next Steps

Increasing global access to biosimilars has the potential of increasing patient access to important, highly effective biological treatments; however, the cost and time associated with biosimilar development remains a significant challenge. One of the primary contributors to the cost is the routine conduct of CES. Therefore, reassessment of the added value of CES presents a singular and immediate opportunity to reduce costs and enhance the efficiency of biosimilar development.

Throughout this workshop, stakeholders identified opportunities to streamline the use of CESs for biosimilar development. Both regulators and industry experts recognized the limitations of these studies. They broadly agreed that CES are not sensitive enough to detect anything but very large analytical differences between proposed biosimilars and RPs, and a very large analytical difference would likely cause a proposed biosimilar to not be able to meet the "highly similar" standard based on analytics alone. Therefore, CES are not likely to be additionally informative with respect to the small differences typically observed in analytical comparisons, particularly if comparative PK show similar profiles between a proposed biosimilar and its RP.

While there are prospects for streamlining CES requirements, both regulators and industry experts identified and discussed challenges that must be addressed to advance further. A key challenge facing both industry and regulators is the timing issues arising from stepwise approach to biosimilar development historically recommended by regulatory guidelines. Working from an implicit default that a CES is expected, biosimilar developers tend to embark on these studies as early as possible in a BDP, because these studies take a long time to complete. From the regulatory perspective, the stepwise approach calls for understanding what uncertainty needs to be resolved based on analytical differences, and it is difficult to make this assessment early in development, when there may only be small scale production lots of the proposed product available. As a result, regulators may not be comfortable providing definitive recommendations on whether a CES is needed or not because of the limited data available early in development. One way to address timing issues may be to utilize a risk-based framework to characterize when CES may be more likely to be helpful. Another key challenge to streamlining is an expectation or preference for clinical data among patients, prescribers, and even some regulatory stakeholders, as well as a lack of detailed understanding about the comparative analytical assessment and the limitations of clinical data.

In summary, there was general convergence among attendees around re-examining the need for CES. Multiple potential next steps and future directions were discussed: (1) regulatory harmonization of a framework for streamlining BDPs, (2) educational efforts to increase awareness of the rigor and role of analytical studies that support biosimilar approval, and (3) opportunities to enhance scientific understanding of the relationship between product QAs and clinical performance. As the biosimilar landscape continues to evolve, it is also critical to continue discussions through forums such as this workshop regarding potential strategies to streamline BDPs. To this end, regulator stakeholders suggested the value of a summary report and/or a white paper to continue efforts toward regulatory convergence on a framework for streamlining biosimilar development, potentially reducing the time and cost of development and ultimately enhancing global accessibility to vital biological treatments. This summary report is a next step in what will be ongoing efforts moving forward.

Appendix

4.1. ACRONYMS

Table 3: Acronyms and Corresponding Definitions

Abbreviation	Definition
ANPP	Agency of Pharmaceutical Products
BDP	Biosimilar Development Program(s)
BPCI	Biologics Price Competition and Innovation
BWG	Biosimilars Working Group
BWG	Biosimilars Working Group
CES	Comparative Efficacy Study(ies)
CMC	Chemistry, Manufacturing, and Controls
EMA	European Medicines Agency
EU	European Union
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factor
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPRP	International Pharmaceutical Regulators Program
MEB	Medicines Evaluation Board
mAbs	Monoclonal Antibodies
MOA	Mechanism of Action
PD	Pharmacodynamic
PK	Pharmacokinetic
QA	Quality Attributes
QTPP	Quality Target Product Profile
ROA	Route of Administration
RP	Reference Product
WHO	World Health Organization

4.2. PARTICIPATING ORGANIZATIONS

Table 4: Organizations Represented at the Public and Regulatory Sessions

Participating Organizations*			
2seventybio	CLT Drug Testing	Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense	Premier Research
3ive Labs, LLC	Codagenix	Jordan Food and Drug Administration	Prevision Policy
3M of Brasil	Cohance Lifesciences	Jordan University of Science and Technology	Privada
Aaps	Coherus Biosciences	Jordanian Association of Pharmaceutical Manufacturers (JAPM)	ProbioMed
Abbott	Community Pharmacy	JSS Academy of Higher Education and Research	Pronamed
AbbVie	CompositePharma	JSS College of Pharmacy	PROPHAR S.A.
ABC	Concept Clinical Services	Julphar Gulf Pharmaceutical Industries Manufacturers	ProPharma Group
Abdi Ibrahim Pharmaceuticals	Consultlmz	K.B. Institute of Pharmaceutical Education and Research	Propharma Medical Supplies
Abraxeolus	Continuing Developmental Services Rx	Kashiv Biosciences LLC	PT Kalbe Farma
Academy of Managed Care Pharmacy	Cooper Pharma	KCAS Bioanalytical & Biomarker Services	Purdue University
Accord-healthcare	COPD Foundation	Kemwell Biopharma	PureTech Health
Accutest Research Labs	Croatian Agency for Medicinal Products and Medical Devices*	Keymed	Purini Capital
Acdima biocenter	CRO-Gsap	King George's Medical University	QDraft
ACE	CuraTeQ Biologics	King Saud University	Quatro Bioanalytical
ACHE	Daewoong Pharmaceutical	Kira Mounier	QuatroBio
Aché Laboratórios Farmacêuticos	Daiichi Sankyo	Kite Pharma	Rafarm SA
ACI Limited	Danish Medicines Agency*	Kosovo Medicines Agency	Reata Pharmaceuticals, Inc.

*Indicates organizations represented at the regulators sessions.

Participating Organizations*			
Activian	Data Science Institute	KPMG Global Services	Regulatory Guidance Group, LLC*
Adalvo	DataRevive	Krishna Institute of Medical Sciences	Relay Therapeutics
Adimed	Datazymes	Ku leuven	Reliance Life Sciences Ltd
ADMA	Datwyler Pharma Packaging	Kymanox	RemeGen Biosciences
ADMERUS	DB Desarrollos Farmaceúticos	Kyowa Kirin	Renaissance Lakewood LLC
Admerus Biosciences	DDReg Pharma	Labcorp	Repare Therapeutics
Advanz Pharma	Deallus Consulting	Laboratorio Elea	Republic of China Food and Drug Administration
Aegros	Deciphera Pharmaceuticals	Laboratorios AC Farma SA	Revive Rx
AEMPS*	Descign	Laboratorios La Santé S.A	Rho
AET Laboratories	Deva Holding	Laboratorios Legrand S.A.	Richter
AffaMed Therapeutics	Directorate General of Drug Administration, Bangladesh	Laboratorios Liomont	Rio Biofarma Brasil
Agencia Española de Medicamentos y Productos Sanitarios*	Diteba Laboratories Inc.	Laboratorios Pisa	RML
Agency for Care Effectiveness	Dokka	Laboratorios Pisa, S.A. de C.V.	Roche
Agency for Medicinal Products and Medical Devices of Croatia*	Dong-A ST	Laboratorios Richmond	Samsung Bioepis
Agenzia Italiana del Farmaco*	Dr Reddy's Laboratories	Lachman Consultants	Sana Pharma
Austrian Agency for Health and Food Safety*	Drug Regulatory Authority of Pakistan	Lambda Therapeutic Research	Sandoz
American Health & Wellness	Drug Testing Laboratory Punjab	LCWang Regulatory Consulting LLC	Sanofi
AIS Health	Duke-Margolis Center for Health Policy	Learn and Confirm Inc	Sanofi Winthrop Industrie
AIV Pharma Engineering México	Dutch Medicines Evaluation Board*	LEO Pharma	Sanzyme
Ajanta Pharma	Eastern Research Group Inc.	Lextro Bio Solutions	Sartorius
Akdeniz University	Ecolab Inc	LIBBS Farmaceutica Ltda	Saudi Food and Drug Authority*
Albedo Consulting Sàrl	Edelman	Lotus Pharma	Saya Bio

Participating Organizations*			
Alembic Pharmaceuticals Ltd.	EG Pharmaceuticals	Lumosa	Scientific Centre for Expert Evaluation of Medicinal Products
Aleon Pharma International	Ege University Faculty of Medicine	Lupin Limited	Scienture Inc.
Alfa Pharmaceuticals Limited	Egyptian Drug Authority*	Luye Pharma Group	Sciton Inc
Ministry of Health of Algeria	EirGenix, Inc.	Ivye	Seagen
Alkem Laboratories Limited	Eli Lilly and Company	mAbxience	Sedulo Group
Allucent	EMD Serono	Mak	Serum Institute of India
Alora Pharmaceuticals	EmPartners	Malta Medicines Authority*	Servier
Altasciences	Enanta Pharmaceuticals	Manila Doctors Hospital	SGT University
Alvotech	enBloom Media, LLC	McCowen Analytical Contract Labs	Shandong Boan Biotechnology Co., Ltd.
Amarex Clinical Research, LLC	Endpoints News	McKesson	Shanghai Henlius Biotech
Amega Biotech	Enem Nostrum Remedies Pvt. Ltd	MD Anderson Cancer Center	Shilpa Biologicals
American College of Rheumatology	Enzene Bioscience	medac GmbH	Shilpa Pharma Inc
American Heart Association	EPIC Clinical Research Organizations	MediaSource	Silanes
American Regent Inc.	Epic Pharma	Medica	Similis Bio
Amgen Inc	Epidemiología & HTA	Medical Faculty Mannheim	Singbio
Amneal Pharmaceuticals Ltd.	ERG Clinical	Medicamenta	Solaris Pharma
Amphastar	Ergomed	Medicines and Healthcare products Regulatory Agency, UK	Sout Healthcare
AnHeart Therapeutics	Estudio Rodrigo	Medicines Evaluation Board (MEB), Netherlands*	South African Health Products Regulatory Authority*
Anteris by Kymanox	Etana Biotechnologies	Medicines for Europe	Spanish Agency of Medicines and Medical Devices*
Anvisa*	Eurofins Donor & Product Testing, Inc.	Medistik	Spanish Biosimilar Medicines Association
Apobiologix	European Medicines Agency*	Meitheal Pharma	Springer Nature

Participating Organizations*			
Apotex Inc.	Eva Pharma	Merck	St Joseph's Home (Catholic Welfare Services, Singapore)
Apothecary's Health Products Retailing	Everest Clinical Research	Merck Sharp & Dohme Federal Credit Union	Stada Arzneimittel
Apsen Farmacêutica	ExCulture	Merz Pharmaceuticals LLC	Stanford School of Medicine
Arab Lab Scientific	Exeltis Colombia	Metrum Research Group	Star Health Network
Arthritis and Rheumatology Clinics of Kansas	Extrovis AG	Michigan Department of Health & Human Services	State Agency of Medicines of the Republic of Latvia*
Ari Pharmaceutical Company	Eyenovia	Micro Labs Ltd	State Institute for Drug Control (SUKL), Czech Republic*
Arnold Ventures	Faegre Drinker Biddle & Reath LLP	MiGenTra Egypt	Statmundo
Arriellos.r.o.	Federal Agency for Medicines and Health Products of Belgium*	Ministry of Education of Greece	Stelis Biopharma Ltd.
Arven İlaç	Federal Commission for the Protection Against Sanitary Risk of Mexico*	Ministry of Food and Drug Safety	Summit Therapeutics
Arvinas	Federal Trade Commission*	Ministry of Food and Drug Safety of Korea*	Sun Pharma Advanced Research Company
Asociación Nacional de Fabricantes de Medicamentos	Ferring Pharmaceuticals, Inc.	Ministry of Health of Brazil	Sun Pharmaceuticals Industries Limited
Asphalion	Fidia Pharma USA Inc.	Ministry of Health of Israel*	Sunpharma
Assure Healthcare Consulting W.L.L.	Finnish Medicines Agency*	Ministry of Health of Peru	Sutter Health System
AstraZeneca	FLAG Therapeutics, Inc.	Ministry of Health of Singapore	Swedish Medical Products Agency*
Atlantic Lifesciences Limited	FlexWare	Ministry of Health, Labour and Welfare of Japan*	Swiss Agency for Therapeutic Products
Atyan, LLC	U.S. Food & Drug Administration*	MJ Biopharm	Syneos Health
Aurea Flores Consultants, LLC	Food and Drug Administration of the Philippines	MJ Biopharm Pvt Ltd	Syngene International Ltd
Auriga Research Pvt Ltd	Formosa Laboratories, Inc.	Molekule Consulting	T Gwise Consulting LLC

Participating Organizations*			
Australia Therapeutic Goods Administration	Formycon AG	MS Pharma	Tabuk
Austrian Medicines and Medical Devices Agency	Fortrea	MSK Pharma	Taiwan Food and Drug Administration*
Autonomous University of Barcelona	French National Medicines Safety Agency (ANSM)*	Mylan Laboratories Limited	Takeda Pharmaceuticals
Avalere Health	Fresenius	Natco Pharma	Tata Consultancy Services
Avantor	Fresh Graduate	Natioanl Institute for Health and Care Excellence of the United Kingdom	Taylor's University (Lakeside Campus), Malaysia
Axantia	Freyr	National Agency for Food and Drug Administration and Control, Nigeria	TDG, Inc.
Axis Clinicals	Fujifilm Kyowa Kirin Biologics	National Agency for Medicines and Medical Devices, Romania*	Tech Observor
Azimuthal Medicals Ltd	G7 Synergon	National Agency of Pharmaceutical Products (ANPP), Algeria	Tecnológico espíritu Santo
B.R. Nahata College of Pharmacy	Gambro Dasco SpA	National Cancer Institute	Tercero en Servicios de Riesgos Sanitarios, SAPI de CV
B.V. Amsterdam Medical & Scientific Alliance	Gandhi Institute of Technology and Management	National Health Regulatory Authority Bahrain	Teva Pharmaceuticals
Bank of America	GC Corporation	National Institute for Innovation in Manufacturing Biopharmaceuticals	Texas Department of State Health Services (DSHS)
Biomedical Advanced Research and Development Authority	Gedeon Richter	National Institute of Health Sciences, Japan	Texas State Board of Pharmacy
Bayer AG	Genentech	National Institute of Pharmaceutical Education and Research, Ahmedabad	The ALS Association
BBU Pharmaceuticals	General Directorate of Medicines, Supplies and Drugs (DIGEMID)	National Institute of Pharmacy and Nutrition (OGYÉI), Hungary*	The Biosimilars Forum
Beacon Pharmaceuticals	Generics Bulletin	National Institute of Pharmacy and Nutrition, Hungary	The Center for Biosimilars
Becton, Dickinson and Company,	Genext Genomics	National Institutes for Food and Drug Control	The Doctorpreneur Academy

Participating Organizations*			
Bell Potter	Genfit	National Institutes of Health	The Kinetix Group
BeonBiz Solutions	Gensci	National Medicines and Food Administration, Asmara, Eritrea	The Pink Sheet
Bharat Serums and Vaccines Ltd.	German University in Cairo	National Multiple Sclerosis Society	The University of Iowa
Biocon Biologics	Gilead	National Organization for Medicines of Greece*	Thea Pharma Inc.
BioFactura Inc.	Glenmark Pharmaceuticals	National Pharmaceutical Regulatory Agency of Malaysia*	Therapeutic Goods Administration, Australia*
BioFrey	Global Regulatory Affairs	National Psoriasis Foundation	Thermo Fisher Scientific
Biogen	Globalpharma	NDA Group	Third World Network
Biologics and Biosimilars Collective Intelligence Consortium	Glycoera Inc	Netherlands Organisation for Applied Scientific Research	Torrent Pharmaceuticals
BiomX	Grand Life Sciences Co. LTD.	Neuralina Therapeutics	TPIreg
Bionovis	Granules India Limited	Ninguna	TPR-group
Biopharma Excellence	Grow Capital, Inc.	Nivagen	Truveta
Biopharma Services Inc.	Grupo Somar	Nobel Ilac	TS Pharma Experts LLC
BioPharmaLogic	Guru Nanak Khalsa College of Arts, Science & Commerce	Norwegian Medicines Agency*	Tulare County Health & Human Services Agency
Biosimilar Biostatistics	Haihe Biopharma	Novartis	U.S. Customs and Border Protection (CBP)
Biosimilars Canada	Haima	Novartis Sandoz Pharma AG	UCHealth
Biosimilars Consultancy	Hastings Toxicology Consulting LLC	Noven Pharmaceuticals, Inc.	Ultra Laboratorios
Biosimilars Nederland	HCG Cancer Centre	NovoNordisk	United BioSource LLC
Biosimilars Review & Report	Health Canada*	Novotech CRO	United Therapeutics Corporation
BioSourcing	Health Products Regulatory Authority (HPRA) of Ireland*	Novum Pharmaceutical Research Services	Universidad Autónoma Metropolitana
Biotec Regulatory Consulting GmbH	Health Sciences Authority of Singapore*	NPS DO BRASIL	Universidad Nacional Autónoma de México
Biotech	HealthVerity	NuCana plc	Universidad Nacional de Colombia
Biotech Consultancy	Healthyfi Group	OBI Pharma, Inc.	University of Alberta

Participating Organizations*			
Biotech Research Group	Henlius	Ocugen Inc.	University of Arizona
Biotechnology Innovation Organization	HepQuant	Office for Registration of Medicinal Products, Poland*	University of Buenos Aires
Bio-Thera Solutions	Hetero Biopharma Ltd.	Olon Group	University of Houston
Biotimize	Hisense	Omega Laboratories	University of Illinois
BioWorld	Howard University	Omeros	University of Karachi
Blau Farmacêutica	Hypera Pharma	Oncord, Inc.	University of Lucerne
Boehringer Ingelheim Pharmaceuticals Inc.	Icelandic Medicines Agency*	Optaine.com	University of New Hampshire Franklin Pierce School of Law
Booz Allen Hamilton*	ICON plc	Optinose	University of Nigeria Nsukka
Boston Clinical Research Institute	IGABIO LLC	Optum	University of Rochester Medical Center
Bracco Diagnostics	IKP Knowledge Park	Orbicular	University of Southern California
Brainfarma	Ilko Biopharmaceuticals	Organon	University of Zurich
Brazilian Health Regulatory Agency*	ILKOGEN	Organon & Co.	U.S. Pharmacopeia
BriaCell Therapeutics	IMAGINutrition. Inc.	Organon Co., Ltd.	USV Private Limited
Brigham and Women's Hospital	Immuneel Therapeutics Pvt Ltd	Organon Pharma	VACSERA
Bristol Myers Squibb	Impacta Serviços em Saúde	Oryzogen	Vaginal Biome Science
BSA Pharma Inc.	INAME-ANMAT	Oxford Medwell Academy	Valerius Biopharma AG
BTS Group	Indonesian Food and Drug Authority	P.K. Narang Strategic Consulting, LLC	VBC Team GmbH
Bycus Therapeutics	InflaMed Inc	Pace Laboratories	Vectura
C&D Regulatory	Innomar Strategies, Inc.	Parexel	Veranex
Cadila Pharmaceuticals Ltd.	Innovation Communications Group Inc.	Paul-Ehrlich Institute*	Verily
California Department of Public Health	Inside Health Policy	Penn Medicine	Viatris
Cambridge Healthcare Research	Insight Advice & Solutions	Penn State Cancer Institute	Vida Consulting
Canadian Generic Pharmaceutical Association	Insight Biologics LLC	Pergament and Cepeda LLP	Vir Biotechnology
CANbridge	Instituto Butantan	Pfizer Inc.	Visual Intelligence, LLC

Participating Organizations*			
Capricor Therapeutics	Instituto de Salud Pública de Chile	Pharmaceutica	Voisin Consulting Life Sciences (VCLS)
Capstone Development Services	Instituto Nacional de Cancerología	Pharmaceutical Research and Manufacturers of America (PhRMA)	Wanya LifeSciences Pvt Ltd
Carexso	Insud Pharma	Pharmaceuticals and Medical Devices Agency of Japan*	Waters Corp
CBCC Global Research	Intas Pharmaceuticals	Pharmaceuticals and Medical Devices Agency of Turkey*	WBB Securities
Celerion	Intech Biopharm	Pharmacosmos A/S	Wellington
Celero	Ipa Laboratories Ltd	Pharmacy and Poisons Board of Kenya	Wockhardt Ltd.
Celltrion	Ipca Laboratories Ltd	PharmaLex GmbH	World Health Organization (WHO)
Celon Pharma	IQVIA	Pharmasia Limited	Wuhan Healthgen Biotechnology Corporation
Center for Drug Evaluation, Taiwan*	Israel Ministry of Health*	Pharmathen SA	Xbrane Biopharma
Center for State Control of Medicines and Medical Devices	Italian National Institute of Health	Pharmet	Xeris Pharmaceuticals
Central Drugs Standard Control Organisation	Italian Medicines Agency (AIFA)*	Pharmetheus	Yung Shin Pharm. Ind. Co., Ltd.
Centre for Innovation in Regulatory Science	ITB-MED	Philippine College of Pharmacetucal Medicine	Zarqa University
Centre for Process Innovation Limited	iYOU Health	PiSA Farmacéutica	Zeal Academy
Certara	Jakob and Partners LLC	Pistevo Law LLC	ZebraSci
Chiesi Farmaceutici	Jamia Hamdard University	Pliant Therapeutics, Inc.	Zeta Pharma
CinnaGen	Jamjoom Pharma	POINT Biopharma	Ziauddin University
Cipla	Janssen	POLITICO	Zoetis
Cliantha Research	JCR Pharmaceuticals Co., Ltd.	Polpharma Biologics	Zydus
ClinChoice	Jehangir Clinical Development Center (JCDC)	Pooyeshdarou	Zydus Life Sciences Limited
Clinergy Health	Jerusalem Pharmaceuticals	PPL	-
Clinnex Research Pvt.Ltd.	Johnson & Johnson	Premier Consulting	-