INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

Embracing Science with Confidence: **Adopting the Revised 2022 WHO Biosimilars Guideline**

An IGBA Biosimilars Committee White Paper

November
2022

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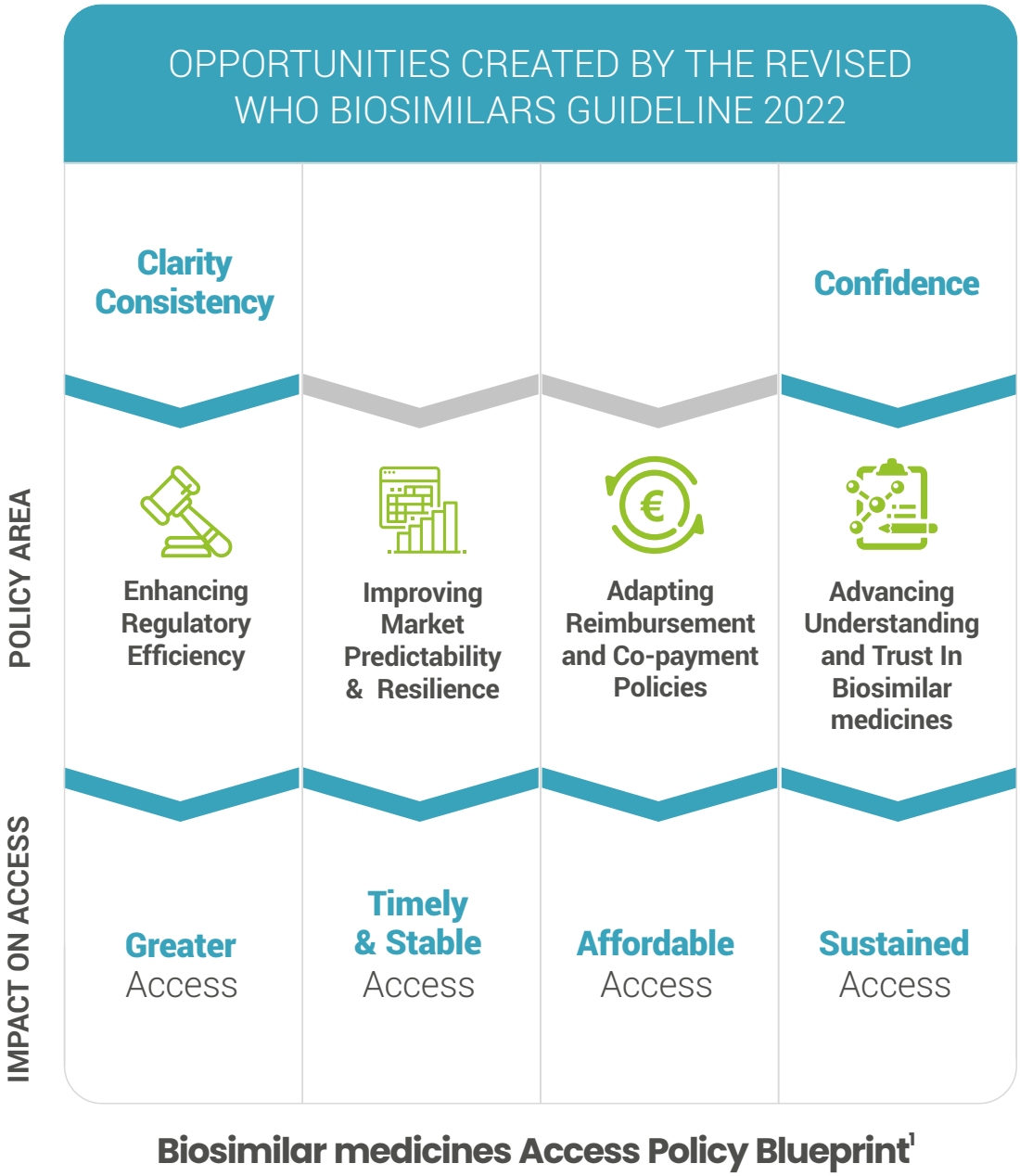
KEY MESSAGES

Biosimilar medicines hold the potential to enable equitable access to biologic therapies for patients around the world. The IGBA's 2021 Biosimilar medicines Access Policy Blueprint[1] identified four key areas where global collaborative action can help achieve the potential for biosimilar medicines.

This paper further elaborates on one of the key areas: Enhancing Regulatory Efficiency for Greater Access.

It discusses how the revised 2022 WHO Biosimilars Guideline[2] (the Guideline) provides a timely opportunity to collectively re-evaluate the way in which regulatory requirements can better advance biosimilar access. The Guideline defines globally acceptable principles for licensing biological products that can be used to harmonize biosimilar medicines regulations around the world. If cohesively adopted by national regulatory authorities, the Guideline can promote more efficient regulatory systems to provide patients with earlier access to safe, effective, high-quality, and lower-cost biosimilar medicines.



Biosimilar medicines Access Policy Blueprint[1]

(1) Effective Strategies to Advance Access to Biologic Therapies for Non-Communicable Diseases – A Biosimilar medicines Access Policy Blueprint (2021) https://www.globalbiosimilarsweek.org/2021/doc/A-Biosimilar-medicines-Access-Policy-Blueprint-IGBA.pdf

(2) For efficiency, this paper will refer to the World Health Organization's (WHO) "Guidelines on evaluation of biosimilars" document finalized in April 2022 as the "WHO Biosimilars guideline" or the "2022 WHO Biosimilars guideline." That document is available here: https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/annex-3---who-guidelines-on-evaluation-of-biosimilars_22-apr-2022.pdf

2022 WHO Biosimilars guideline: Advances in scientific knowledge and experience

HIGHLIGHTS

- The revised 2022 WHO Biosimilars Guideline reflects an updated vision for efficient and streamlined biosimilar medicines regulatory assessments, consistent with advances in biologic regulatory science and extensive experience with biologic therapies, including biosimilar medicines.
- Key updates in the revised Guideline:
    1. a limited, exception-based approach towards animal studies
    2. a streamlined approach to considering clinical comparability requirements
    3. a simplified approach to the sourcing of comparator products

A robust biosimilar development regulatory framework

Since it was first published in 2009, the WHO Biosimilars Guideline[3] has served as a useful tool for health authorities in shaping biosimilar regulatory and policy frameworks. The consistency and rigour of the approach outlined in the WHO Biosimilars Guideline has enabled authorities around the world to approve quality, safe, and efficacious biosimilar medicines for patients who otherwise would have lacked access.

> **The WHO [Biosimilars] Guideline has contributed significantly to setting the regulatory framework for [biosimilars] within WHO countries, increasing international regulatory convergence and improving consistency in the terminology used in the evaluation of [biosimilars].[4]**

Following a rigorous consultation process, the 2022 WHO Biosimilars Guideline was adopted in April 2022.

This revised Guideline confirms the overall robustness of the biosimilar development framework, while making key updates in line with evolving scientific understanding.

KEY UPDATES

1.Limited, exception-based approach to the use of animal studies

The 2022 WHO Biosimilars Guideline has been updated with new guidance on in vivo animal studies, in line with implementation of the '3Rs Principles' ("Replace, Reduce, Refine"). The goal of this guidance is "*to minimize the use of animals in testing*". The Guideline affirms that "*the need for additional in vivo animal studies would be expected to represent a rare scenario*."[5]

Regulatory experience suggests that "state-of-the-art analytical and *in-vitro* functional testing and robust pharmacokinetic and pharmacodynamic studies are sufficient to demonstrate biosimilarity."[4] In the vast majority of cases, pre-clinical animal studies would not add new information to the regulatory decision-making process and are no longer regarded a pre-requisite before entering clinical testing. Indeed, regulatory frameworks in some jurisdictions, such as Europe and Canada, already reflect that "*in vivo toxicological studies are generally not needed…[and] usually [have] no relevance for comparing two highly similar biological products with a well-known active substance*."[4]

(3) Several changes were made to the 2009 version of the WHO Biosimilars Guideline in the 2022 revision. One foundational update was to align on use of the term 'biosimilar' rather than 'similar biotherapeutic product (SBP)', in line with coalescing global practice over the last decade. Consistency in terminology is critical to establishing a shared understanding and regulatory approach globally. This paper will refer to both versions as the WHO Biosimilars Guideline to reflect continuity with the current title, instead of distinguishing the prior version as the SBP guideline.

(4) Kurki et al. Regulatory Evaluation of Biosimilars: Refinement of Principles Based on the Scientific Evidence and Clinical Experience https://link.springer.com/article/10.1007/s40259-022-00533-x (2022)

(5) WHO Biosimilars Guideline https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/annex-3---who-guidelines-on-evaluation-of-biosimilars_22-apr-2022.pdf (2022)

2. Streamlined approach to clinical efficacy & safety comparability requirements

The 2022 WHO Biosimilars Guideline presents considerations related to the "*amount and type of clinical data required*" for biosimilar evaluation, noting that different clinical approaches are possible to demonstrate comparability.

> The Guideline states that a "**comparative efficacy and safety trial will not be necessary** if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise"[5]

The Guideline outlines factors that influence the need for a confirmatory comparative clinical efficacy and safety study. Notably, the listed factors are broader than whether a suitable PD marker exists, including how well the biosimilar can be characterized, the degree of understanding of the mechanism of action, and the degree of analytical and functional similarity between the biosimilar and the reference product.

Based on advancement in analytical and functional testing over the last decade and the knowledge gained in development and evaluation of multiple additional biological molecules, confidence in the quality, safety, and efficacy of a proposed biosimilar can be achieved in most cases without a comparative clinical efficacy and safety study. The foundational components of biosimilar development are analytical characterization, comparative *in vitro* functional testing and pharmacokinetic (PK) studies, while comparative clinical efficacy and safety studies are confirmatory.[4] The purpose of confirmatory comparative clinical studies is to address residual uncertainty, "*the degree of [which] may not be as high in 2021 as it was at the time of the publication of the WHO guidelines in 2009.*"[4]

3. Simplified approach to the sourcing of comparator products

The 2022 WHO Biosimilars Guideline makes clear that the use of a non-local reference product as comparator is acceptable. The Guideline notes that it is "*not always…feasible or necessary*" to use a nationally authorised reference product for biosimilar development, and that in practice, use of a non-locally sourced reference product as comparator is already allowed in several jurisdictions. The Guideline presents considerations to enable National Regulatory Agencies (NRAs) to implement this in

Want to know more?

- WHO (2022) - Revised WHO Biosimilars Guideline (link)
- Kurki, P. (2022) - Regulatory Evaluation of Biosimilars: Refinement of Principles Based on Scientific Evidence and Clinical Experience (link)
- Wadhwa, M. (2022) – Meeting Report WHO informal consultation on revision of guidelines on evaluation of similar biotherapeutic products, virtual meeting, 30 June – 2 July 2021 (link)
- Kang, HN. (2021) - Regulatory challenges with biosimilars: an update from 20 countries (link)
- Kang, HN. (2020) - The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019 (link)

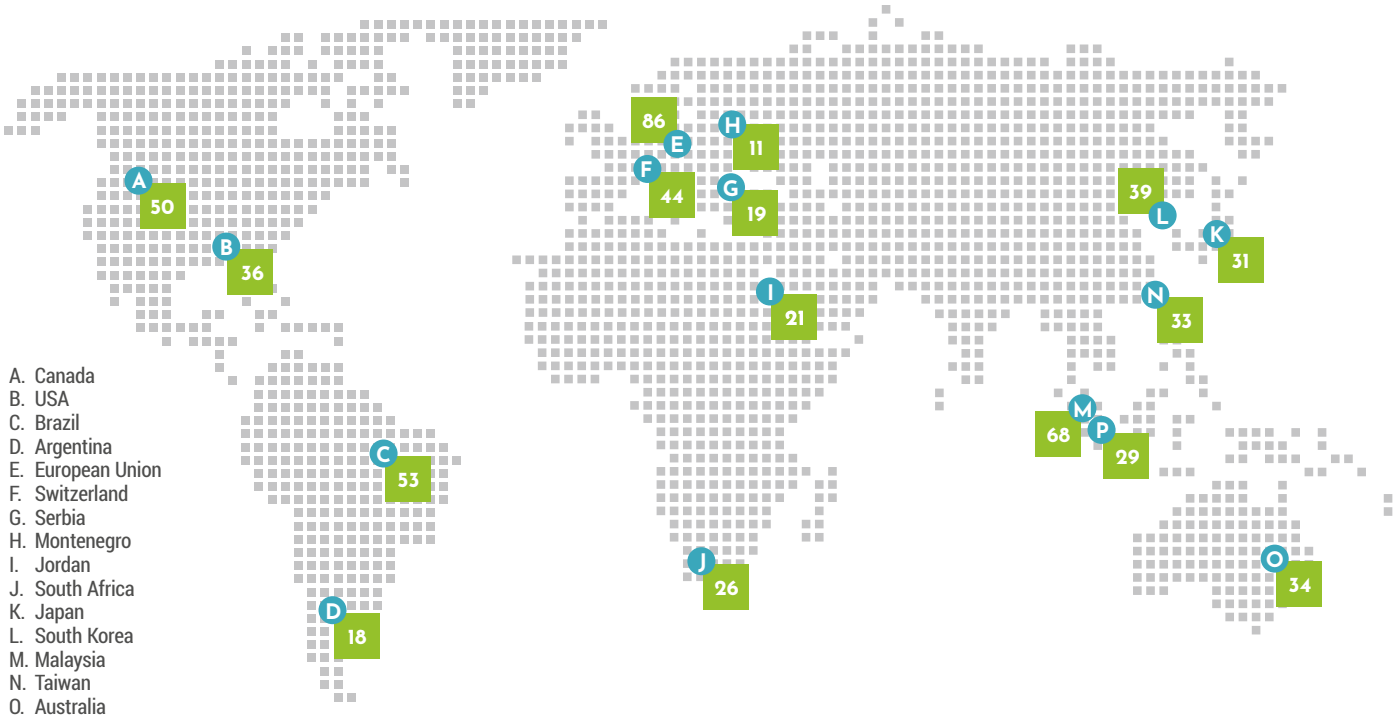
practice, including requiring the comparator product be authorised in a jurisdiction with a well-established biologics evaluation and surveillance framework.[5]

The revision of the WHO Biosimilars Guideline reflects the evolution in practice over the last decade for NRAs to increasingly accept the use of a non-local reference product as comparator, with no concerns observed to date. Key to the Guideline update is inclusion of the element of 'necessity', beyond 'feasibility', in considering use of a locally authorised reference product as comparator. The 2009 WHO Guideline created flexibility based on feasibility for jurisdictions with no reference product authorised locally. The 2022 revision articulates the understanding that even if use of a local reference is feasible, it may not be necessary. It acknowledges that if every jurisdiction required locally-sourced reference then studies would have to be repeated for each, whereas the underlying clinical data package would be the same globally. This principle is foundational to the Guideline revision – re-evaluation is needed of what is necessary to better "*harmonize global requirements, and lead to easier and speedier approval and assurance of the quality, safety and efficacy of [biosimilars]*".[5]

Shifting towards the latest scientific evidence

The Guideline's key updates are supported by scientific advancements and the extensive clinical experience with biosimilars gathered since the 2009 version was published. With safety data from 1 million patient-treatment years in Europe alone[6] and over 500 biosimilar approvals (2022)[7] globally, regulatory knowledge and experience has significantly grown over the years. This revision provides greater clarity on science-based, flexible approaches towards quality, nonclinical and clinical evaluation of biosimilar medicines.

Biosimilars approved worldwide[7]



A. Canada
B. USA
C. Brazil
D. Argentina
E. European Union
F. Switzerland
G. Serbia
H. Montenegro
I. Jordan
J. South Africa
K. Japan
L. South Korea
M. Malaysia
N. Taiwan
O. Australia
P. Singapore

(6) EMA/HMA Statement onthe scientific rationale supporting interchangeability of biosimilars in the EU (Sept 2022) https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged

(7) IGBA Biosimilars Communication Module 6 https://www.igbamedicines.org/doc/20220808_Module6.pdf

The revision reflects the shift in approach this experience allows: **a renewed focus on targeting specifically the data necessary for a confident determination of the quality, safety, and efficacy of a biosimilar medicine, and removing requirements that may be familiar, or even helpful, but are not necessary**. The evolution in the nature of evidence to be generated is supported by science and experience to ensure the highest level of relevant evidence is provided to regulators in the assessment process.

1) Advances in analytical technologies and techniques have enabled biosimilar medicines developers to better characterize molecules, in many cases far better than when the initial biologic therapy (reference product) was characterized. **With new analytical methods comes an opportunity to shift medicines development away from ethically questionable, costly, and time-consuming animal and human trials**. Consistent with a benefit-risk approach to medical research and with the Helsinki declaration[8], advances in analytical methods have enabled more efficient and ethical options for development of biosimilars.

Regulatory efficiency opportunities created by the revised WHO biosimilars guideline 2022[1]

(8) See, in particular, in item 16: "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects."
(9) Schiestl M, et al. The path towards a tailored clinical biosimilar development. https://link.springer.com/article/10.1007/s40259-020-00422-1
(10) Bielsky MC, et al Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial, https://doi.org/10.1016/j.drudis.2020.09.006 (2020)
(11) Webster C., et al (2021) Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance https://link.springer.com/content/pdf/10.1007/s40259-021-00488-5.pdf

2) Experience shows that, in addition to ethical concerns with unnecessary animal testing, inflexible requirements for in vivo testing add time and cost to biosimilar development, while providing no apparent benefit. Uniform implementation of the 3R Principles in the context of biosimilar evaluation is fully in line with evolving scientific understanding and experience in markets where biologic regulatory assessment experience is the greatest. NRAs can feel confident requiring in vivo animal testing only in exceptional, scientifically justified situations, and reflect in local frameworks a clear articulation that in vivo testing is not required and indeed, should be discouraged.

3) A global shift in regulatory perspective about comparative clinical efficacy and safety studies from a default requirement to a case-by-case need, based on assessment against clear parameters, could dramatically impact the time and resources required to develop a biosimilar, paving the way for speedier access. Research has shown that large confirmatory efficacy and safety studies are generally not needed to establish biosimilarity, including for monoclonal antibodies.[9,10]

The WHO Biosimilars Guideline articulates that comparative clinical efficacy and safety studies are not scientifically justified by default, when sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise. Building from the factors outlined in the Guideline, regulators could consider defining narrow criteria, harmonized to the extent possible across geographies, to explain when and why these types of confirmatory trials should be conducted.

4) Flexibility in the use of a non-local reference product as comparator for biosimilar development and approval is well-supported scientifically and in practice.[4,11] **Moving towards broad acceptability of a non-local comparator will reduce the need for duplicative development steps, including clinical studies, and speed the availability of biosimilar medicines**. Progress towards acceptability of a single global comparator product could have a profound impact on the ability of biosimilar competition to emerge for all types of biological products, including those for which reference product sourcing and analysis across multiple jurisdictions may present a decisive opportunity. Regulatory authorities can feel confident in accepting a non-locally authorised reference product as a comparator for biosimilar development.

Global adoption: embracing regulatory science with confidence

HIGHLIGHTS

- Regulators can overcome collective challenges by the timely implementation of the 2022 WHO Biosimilars Guideline.
- Efficiency gains in biosimilar regulatory processes have a direct impact on the ability of patients to benefit from timely and affordable access to biologic therapies.

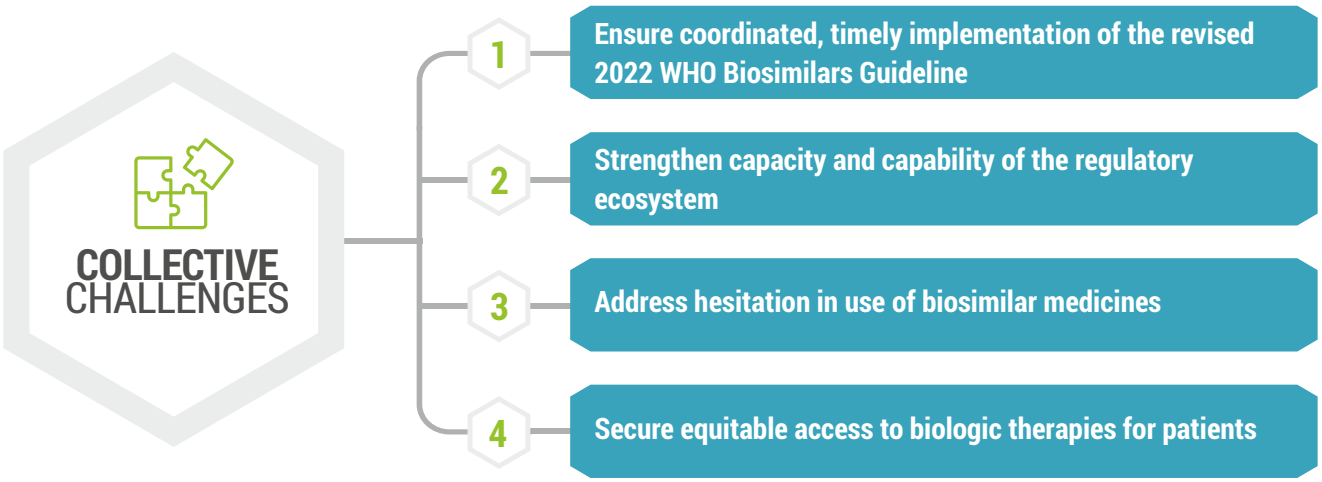
Timely implementation to advance regulatory efficiency

Consistent, timely implementation of the principles outlined in the revised 2022 WHO Biosimilars Guideline is critically important to advancing an aligned global approach towards streamlined biosimilar development and approval. Despite the first WHO Biosimilars Guideline publication in 2009, some countries are yet to actively adopt and implement biosimilar medicines regulatory frameworks in line with the WHO Guideline, more than a decade later. As a result, some authorities approved 'generic' versions of biological products based on data requirements that are unsuitable for the demonstration of biosimilarity and ensuring confidence in quality, safety and efficacy.

The 2022 WHO Biosimilars Guideline is a starting point for the next phase of aligning regulatory requirements for biosimilars globally. It offers an opportunity for health authorities currently lacking biosimilar regulatory frameworks to implement the guideline locally. Regulatory authorities that have already issued their own biosimilar regulation nationally should take this opportunity to re-assess and update their existing norms considering the principles outlined in the revised WHO Biosimilars Guideline.

The international reliance of regulators should also be harnessed to drive the effective implementation of guidelines through the delivery of aligned training and capacity building. The WHO, in partnership with other stakeholders, can play a key role in coordinating these efforts in countries where the biosimilar medicines regulatory framework is still new or under development, through facilitating the sharing of good practices, experience and knowledge exchange.

NRAs should consider both the immediate needs of patients and the long-term regulatory system roadmap when assessing how to utilize tools of international collaboration. Regulatory authorities must consider their responsibility not only to approve quality, safe, efficacious products, but also their responsibility to do so as quickly and efficiently as possible.



Mutual reliance between regulators, including as part of the WHO collaborative procedure, can be further deployed to leverage existing approvals by WHO Listed Authorities in support of approval in another jurisdiction as an efficient way to enhance the timely availability of quality assured medicines. The Caribbean Regulatory System, an initiative of the Caribbean Community and Common Market (CARICOM) represents a leading example of resource-sharing and capacity-building, in support of access to quality-assured medicines.

Global collaboration to promote patient access

In addition to the consistent global adoption of the Guideline, regulatory authorities can further support earlier and broader access to biologic therapies through greater collaboration. **Whether through reliance on assessments, convergence of requirements, or both, regulatory authorities have options available immediately to leverage efficiency for timelier patient access**.

> **Global collaborative action on biosimilar regulatory approaches such as those laid out in the 2022 revised WHO Guideline can help achieve the promise of biosimilar medicines, translating into broader and more sustainable access to biologic therapies.**

More generally, greater international convergence among regulators is needed to align evidence requirements, reduce duplication, and optimise development timelines. Multiple avenues exist for regulatory collaboration and convergence, including the International Council on Harmonization (ICH), the International Council of Drug Regulatory Authorities (ICDRA), the International Pharmaceutical Regulators Programme (IPRP), and numerous bilateral and multilateral groups, such as the ACCESS consortium (Australia, Canada, Switzerland, Singapore and the UK). Coordination across these platforms is critical.

Moving together, quickly and consistently, to adopt aligned principles outlined in the WHO Guideline is important to fully and confidently enable the efficiency gains that can fuel access. As long as geographies diverge in evidence expectations, developers will either need to invest in satisfying the most burdensome requirements or decide not to pursue licensing in some geographies. Enabling investment for efficient biosimilar medicine development programs, particularly by aligning requirements based on the latest scientific understanding, creates room for greater competition on a global scale, which can in turn drive more timely and affordable access for patients. Global collaborative action on biosimilar regulatory approaches such as those laid out in the 2022 revised WHO Guideline can help achieve the promise of biosimilar medicines, translating into broader and more sustainable access to biologic therapies.

Conclusion

> **The revised Guideline provides Clarity, Consistency and Confidence in state-of-the-art regulatory science for biosimilar medicines.**

Biosimilar medicines have the potential to significantly expand patient access to biologic therapies, including those that are lifesaving or have a transformational impact on quality of life but are currently not available to patients in many countries. This access potential can only be realized if barriers to biosimilars are reduced. Current barriers span regulatory, legal, market access and competition elements. Addressing regulatory barriers is a critical first step, and one within immediate reach, based on timely and consistent implementation of the revised WHO Biosimilars Guideline.

The WHO in 2022 took a major step towards enabling more equitable access to biologic medicines with its revised Biosimilars Guideline. **The revised Guideline provides Clarity, Consistency and Confidence in state-of-the-art regulatory science for biosimilar medicines. The WHO's approach reflects a balance of well-established science, broad clinical experience, and recent technological and scientific advances**. In the revision, the WHO articulates its expectation that the clear, globally appropriate, scientific principles outlined in the guideline "will help to harmonize global requirements, and lead to easier and speedier approval and assurance of the quality, safety and efficacy of these products."[5]

Call to Action

The revised 2022 WHO Biosimilars Guideline encourages regulatory authorities to confidently re-evaluate requirements, considering the public health and public policy implications of overly burdensome requirements in limiting patient access to biosimilars. As experts note, "regulators' risk aversion should not suppress the development of important medicines[4]."

Regulators can advance the timely and consistent global implementation of the revised WHO Biosimilars Guideline immediately. A fragmented approach to adopting the Guideline will not result in the efficiency needed to secure broad, quick access to biosimilar medicines.

Building from lessons learnt in rapid regulatory responses to address the unprecedented global challenge of the COVID-19 pandemic, regulatory authorities are well-positioned to mobilize cross-border collaborations to move together towards streamlined regulatory requirements, allowing all to progress with confidence.

THE TIME FOR ACTION IS NOW; PATIENTS ARE WAITING FOR ACCESS TO PROVEN BIOLOGIC THERAPIES.

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ABOUT IGBA

The International Generic and Biosimilar Medicines Association (IGBA), strengthens corporation between associations representing manufacturers of generic and biosimilar medicines around the world. Adopting a patient centric approach, IGBA is at the forefront of globally improving patients' access to quality assured, safe and cost-effective medicines by preserving competition as well as enabling innovation in the pharmaceutical sector and sustainable economic contributions for all stakeholders.

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For more details, regarding IGBA and its member associations, see the IGBA website at: www.igbamedicines.org

For IGBA Biosimilar resources, please see: https://www.igbamedicines.org/committees/biosimilars-committee