



Developing a Regulatory Policy Framework Supporting Biosimilar Competition: The Opportunity for Tailored Clinical Biosimilar Development

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Key Messages

- Biosimilar medicines enable market competition that can improve the cost-effectiveness of biologic therapies and increase patient access to medicine, but competition is constrained by the time and cost associated with biosimilar development.
- Revisiting regulatory requirements for biosimilar medicines in line with scientific advances and accumulated regulatory and clinical experience can facilitate biosimilar approval, an important foundation for competition and access.
- Comparative clinical efficacy studies have limited value in the overall regulatory assessment and decision-making process, yet regulators rarely waive the need to conduct these studies.
- The decision to request a comparative clinical efficacy study should be based on a scientific evaluation assessing whether such a study would add scientific value to a given application.
- A global regulators roadmap towards streamlined biosimilar development program should be adopted, maintaining the scientific and regulatory rigor needed to support approval, and allowing for tailored clinical development.
- The role of regulators extends beyond approval to include education for healthcare professionals to understand the analytical science that underpins biosimilarity, ensuring that regulatory approval translates to utilization of biosimilar medicines.

Introduction

Biologic medicines are complex medicines developed in living cells that offer treatment options for patients suffering from many serious conditions, such as cancer, diabetes and rheumatoid arthritis. Biosimilar medicines are versions of biologic medicines that have no meaningful differences in safety or efficacy/effectiveness and enable competition following resolution of market exclusivity periods. They have vast potential to improve the cost-effectiveness of biologic therapies and provide broader access to medicines for patients.

Health inequities remain significant in communities around the world, across the range of healthcare services and products, and this is particularly true for biologic therapies. Biologics have revolutionized the treatment landscape for many diseases, but at a significant financial cost to health systems and patients. Despite the advent of biosimilar competitors, equity in access to biologic therapies remains a challenge, in large part due to systemic hurdles preventing optimal use of biosimilar medicines.

Policy-makers at all levels can play a role in fostering an environment conducive to maximizing the potential of biosimilar medicines to reduce inequities in healthcare. Biosimilar medicines not only expand access to current treatments previously out of reach for some patients, they also allow health systems to provide increased access to innovative treatments, diagnostics and cures through more efficient use of available funds. The global community has committed to achieving Sustainable Development Goal 3: Ensuring healthy lives and promoting well-being for all at all ages, including reducing by one third premature mortality from non-

About IGBA

The International Generic and Biosimilar medicines Association (IGBA) was founded to strengthen cooperation between associations representing manufacturers of generic and biosimilar medicines from around the world. The IGBA is at the forefront of preserving sustainable competition within our industry, by stimulating competitiveness and innovation in the pharmaceutical sector; thereby, ensuring millions of patients around the world have access to high quality, pro-competitive medicines. For more details, regarding IGBA and its member associations, see the IGBA website at: www.igbamedicines.org.



communicable diseases by 2030.¹ Equitable access to safe, effective, quality and affordable medicines is a critical component of achieving this collective goal. Ensuring that patients get the medicines they need, today and in the future, requires collaboration between all affected stakeholders, including regulatory authorities, pricing and reimbursement agencies, payors, medical societies, healthcare providers and patients.

Regulatory authorities play a central role in creating a sustainable environment for biosimilar medicine development, approval and patient access. Building on their considerable scientific knowledge and cumulative experience with biologic medicines, regulators can expand access to biologic medicines by expediting biosimilar approval and ensuring accurate healthcare stakeholder understanding of biosimilarity to translate approval to appropriate utilization. This can be achieved by coupling tailored clinical development with advanced comparative analytics and educating stakeholders on the quality, safety and efficacy of biosimilar medicines and the comparative utility of analytical and clinical data to support biosimilarity. Adapting the biosimilar development paradigm to encourage tailored clinical development programs will facilitate development of these products by ensuring that the studies are designed to quickly and precisely provide the relevant and definitive data to establish that a biosimilar will have no clinically meaningful difference to the biologic that it is designed to match. This in turn will have a direct impact on the sustainability of biosimilar competition and contribute to increased patient access.

The need for biosimilar medicines – an evolving treatment landscape, ongoing health inequities, and challenges to a sustainable biosimilar market

Biologic medicines are fundamental treatments that address serious health conditions. Innovation in biologic medicines has flourished, resulting in tremendous advances in disease management. Due to the high cost and the extensive use of these medicines, biologic medicines represent an increasing portion of healthcare budgets. Eight of the top ten drugs in 2018 by spending globally were biologics, and sales of these biologics constituted over \$70 billion in 2018 alone.² Biologic medicines represent tremendous innovation but also create a significant challenge for health systems that will only continue to increase as more biologics reach the market.

Due to the high cost of biologic therapies, limitations on access to biologic medicines are increasingly common, even in high-income countries. These restrictions are highlighted by the access expansion observed following introduction of off-patent competition. Upon approval, biosimilar medicines have been shown to unleash the untapped potential of biologic therapies. By making these treatments more cost-effective, they have resulted in the earlier use of biologic medicine in patients' disease progression as medically appropriate, and enabled expansion of treatment to additional patients. For example, prior to biosimilar market entry, the use of filgrastim for primary prophylaxis of febrile neutropenia was deemed clinically effective but not cost-effective in many analyses, leading to coverage policies limiting use. Improved cost-effectiveness following the arrival of biosimilar filgrastim competition allowed for lifting of restrictions on the use of filgrastim for primary prophylaxis in many countries, resulting in dramatic increases in patient access – fivefold increases filgrastim use were documented in the UK and Sweden.³

Biosimilar medicines improve equity in access to biologic medicines, as well as healthcare products and services more generally. The immediate gains for health budgets and patient access from using biosimilar medicines is clear, and yet is only the first step in improving health system sustainability moving forward. The primary benefit of sustained biosimilar competition is the promise of continued cost-effectiveness gains over time. This allows budgetary confidence in adoption of new treatments and expanded use of medicines where clinically appropriate but previously unaffordable. Biosimilar medicines facilitate a redistribution of finite healthcare resources that had been selectively dedicated to patent-protected biological treatments for specific, limited patient populations, to areas of unmet needs or where investments had been limited. Biosimilar medicines are a must-have resource for payors and governments in affording access to innovations, considering the growing portion of therapeutic portfolios and global sales that biologic medicines represent.

The sustained benefit of biosimilar competition is contingent on development of healthy biosimilar markets today. Using biosimilars to drive short-term cost savings at the expense of sustainable competition will foreclose future treatment access. Unfortunately, few health systems are making the necessary policy changes

¹ United Nations Sustainable Development Goals, available online at:

<https://sustainabledevelopment.un.org/sdg3>

² Informa Pharma Intelligence, 'The Evolution of Pharma's Blockbusters,' available online at

<https://pharmastore.informa.com/product/top-10-drugs-biologic-blockbusters-and-the-biosimilar-threat/>

³ Cornes et al 'The evolution of value with filgrastim in oncology,' Future Oncology, Vol 15 No 13, 5 March 2019, available online at: <https://doi.org/10.2217/fon-2018-0762>



today to establish long-term success for biosimilar medicine competition. With limited exceptions, systems have either treated biosimilars as cost-cutting tools, sacrificing sustainable access to biologic medicines for immediate savings, or have not proactively supported biosimilar uptake, opting to continue paying premium prices for originator biologics due to skewed incentive structures and resistance to change. Urgent reflection by policy-makers at all levels is needed to create an environment conducive to long-term biosimilar competition. Absent policy action, biosimilar medicines cannot achieve their promise in reducing health inequities and creating long-term health system savings.

Although the role of biosimilar medicines in affording access may seem analogous to the benefit brought by small-molecule generic medicines, there are important differences to consider in implementing supportive policies for off-patent competition. The development of a biosimilar medicine typically costs between \$100-300 million USD and can take nearly a decade, compared to the vastly smaller traditional development cost of a small molecule generic medicine of around \$5 million USD.⁴ The market dynamics influencing competitiveness of biosimilar medicines are also unique, and successful biosimilar market development requires different policies than those used for traditional originator or generic medicines markets. Because biosimilar development currently involves large resource commitments both in terms of cost and timelines, investment in developing biosimilar candidates under the current regulatory and market framework is limited mainly to blockbuster biologic medicines.⁵ Fostering a competitive landscape for access beyond blockbuster medicines requires optimization of biosimilar development and market dynamics.

There are multiple facets to creating an optimal environment for access to biologic medicines: product development and approval, market authorization and launch, competitive dynamics and uptake. Different stakeholders play critical roles across this spectrum and each segment cannot be viewed in isolation. Regulatory requirements for biosimilar development have an impact on the time it takes to access the biosimilar in all jurisdictions and on the costs of the products when launched. Laws related to intellectual property protection impact the availability of approved biosimilars in some jurisdictions more than others, at times limiting competition for years. Market policies can also inhibit use of biosimilar medicines by reducing the competitiveness of these therapies. In turn, this lowers the return on investment associated with biosimilar medicines, disincentivizing companies from investing further in development of future biosimilars. These elements interact and must be evaluated in conjunction with each other. Further collaborative action is needed to streamline policies across the spectrum of biosimilar development, approval, commercialization and use to maximize the potential of biosimilar medicines to improve health equity for patients. A harmonized regulatory approach can facilitate greater access worldwide to more affordable biologics for all patients.

Role of regulators in creating sustainable access to biosimilars and beyond

Regulatory authorities play a central role in creating and sustaining patient access to biologic medicines. The core function of medicines regulators is to evaluate and approve safe and effective medicines. The framework put in place to do so has a tremendous impact on the sustainability of the sector. Extraneous and unnecessary, and hence potentially unethical, demands limit availability of all medicines.

Although tailored regulatory pathways are already in place for the approval of biosimilar medicines compared to novel originator biologic medicines, fostering a sustainable multi-source medicines environment requires regulators to further streamline regulatory requirements for biosimilar approval. Regulators apply product-specific risk-based approaches that are guided by their many years of experience and utilise large data repositories accrued for reference products and biosimilars alike. Regulators should respond to advances in analytical science that provide more detailed and clinically-relevant information than was possible in the past by encouraging tailored clinical development programs to support approval of biosimilar medicines. Failure to do so risks limiting the ability of biosimilars to provide cost-effective competition to originator biologic therapies.

While the current development paradigm and regulatory approval process has established a high level of confidence in biosimilar medicines, it has become apparent that the requirement to demonstrate comparative clinical efficacy has limited value in the overall regulatory assessment and decision-making process for biosimilarity. Based on a retrospective review, all the comparative efficacy studies of all biosimilar development programs approved in the EU and US determined confirmation of comparative efficacy. In 95% of these biosimilar development programs, the comparative efficacy study added no scientific value to the review

⁴ McKinsey & Company 'Five things to know about biosimilars right now,' July 2018, available online at: <https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/five-things-to-know-about-biosimilars-right-now>

⁵ Blockbuster medicines are typically defined as those with greater than \$1 billion sales annually

process. In the remaining 5% of programs, comparative efficacy was established but differences were observed in immunogenicity rates and manufacturing process improvements were needed before approval could be given. Importantly, these outcomes were observed in biosimilars that were developed prior to 2010, after which time no differences in clinical efficacy and safety including immunogenicity have been observed.⁶ Cumulative knowledge and experience should enable regulators, working in collaboration with industry partners, to develop a roadmap that moves away from routinely requiring comparative efficacy trials to support biosimilar approval. The assessment of quality, safety and efficacy of a biosimilar will remain uncompromised, while contributing to a sustainable multi-source medicine environment. The tone set by regulators is critical – biosimilar medicine development is a resource-intensive endeavour and companies will likely continue to take a conservative approach to approval in the absence of a clear roadmap from regulatory authorities towards tailoring clinical development.

Advances in analytical and functional characterization of biologics has enabled a greater understanding of the critical physicochemical and functional quality attributes and their link to clinical performance. It is also apparent, from testing multiple batches of reference biologics, that there is inherent variability in physicochemical attributes from batch-to-batch. However, this variability is controlled by the manufacturers and accepted by health authorities as not clinically relevant. A globally harmonized comparability guideline for manufacturing process changes for biologics (ICHQ5E) was published in 2003, providing regulators experience in evaluation of product comparability to support approval of these changes. The approach recommended by ICHQ5E is based on comparability studies to establish that materials produced after the process change are highly similar to material produced prior to the process change. Since implementation of ICHQ5E, substantial knowledge has been gained by reviewing vast amounts of data across every type of biological medicine to support virtually every type of manufacturing change. These experiences are directly relevant to assessment of biosimilarity and should be used by all health authorities to inform regulatory requirements for biosimilar approval.

If critical physicochemical and functional quality attributes of the biosimilar candidate are closely aligned to those of the reference product and comparative human pharmacokinetic and, if necessary, additional immunogenicity studies confirm that the biosimilar is equivalent to its reference biologic product, a scientific assessment should be undertaken to evaluate whether requesting a confirmatory comparative efficacy study will add scientific value. This approach is in line with a recent paper from regulatory experts looking into pre-requisites and modalities to streamline biosimilar development⁷. At present, health authorities rarely waive the need to conduct a comparative efficacy study because doing so predominantly requires suitable biomarkers, few examples of which are known and are described in literature. Identification of such biomarkers is a lengthy and resource-intensive process, with no guarantee for success. The situation is made worse by lack of global regulatory consensus on the detailed requirements for appropriate biomarkers. Given scientific advances and the accumulated regulatory and clinical experience with biologic medicines, including biosimilars, the presence of suitable biomarkers should no longer be treated as the sentinel factor in waiving comparative clinical efficacy studies.

Establishing a roadmap to tailored clinical biosimilar development that relies on strong analytical science and human pharmacokinetic data is an important step to more accurately reflect the scientific value brought by elements of the data package. Further opportunities to expedite biosimilar development by building on global experience in support of aligned requirements across jurisdictions include:

- recognizing a global comparator product and eliminating bridging studies between versions of the reference product licensed in multiple jurisdictions;
- preventing unnecessary and unethical enrolment of subjects and patients in local confirmatory comparative efficacy clinical trials when quality, safety and efficacy can otherwise be proven; and
- reciprocal recognition of facility inspections through the establishment of frameworks providing for cross-jurisdictional regulatory cooperation, reliance and good practices.

Facilitating access to biosimilar medicines does not end with regulators' scientific evaluation and approval of the appropriately informative data package. Regulatory agencies play a pivotal role in informing and educating stakeholders about medicines, including biologic medicines and their unique characteristics and inherent variability. This includes information about the regulatory approval process for medicines and how regulatory oversight evolves to accommodate scientific progress. Sharing this experience is critical to ensuring patient and provider trust in medicines. This is relevant not only for the introduction of new molecular entities, but also for biosimilar medicines and for existing medicines with expanded indications.

⁶ Schiestl et al. *BioDrugs* 2020;34, 97–306; <https://doi.org/10.1007/s40259-020-00422-1>

⁷ Bielsky et al. *DRUDIS* 2020 (In Press) ; 2770 1–9, <https://doi.org/10.1016/j.drudis.2020.09.006>



Education is critical in realizing the benefit of tailored clinical development to support biosimilar medicine approval. Physicians are well-versed in clinical data and expect to see clinical studies to support use of newly introduced products, even biosimilar medicines. However, physicians are less familiar with the concept of totality of evidence on which biosimilar development is based, and especially on the key role of comparative analytical testing, despite the shared foundation of comparability used for originator biologic manufacturing changes. Understanding by healthcare professionals (HCPs) of the analytical data that supports establishing biosimilarity can ensure regulatory approval of a biosimilar medicine translates into utilization and access. This trust-building with HCPs is essential if tailored clinical development programs are to be accepted and adopted. Regulators are a trusted voice and must be vocal in supporting the therapeutic equivalence of biosimilar medicines with their reference products. While regulators have taken steps to improve stakeholder understanding of biosimilar medicines, more effort is required to accommodate greater reliance on analytical data over clinical studies once tailored clinical development programs become established.⁸

Conclusion

Tailoring biosimilar development requirements ensures system preparedness for next-generation biologic medicines, particularly targeted treatments that cannot support multisource competition under the existing regulatory, legal and market access frameworks. Changing the biosimilar development paradigm is critical to ensuring a healthy life-cycle of innovation and competition.

Biologic medicines are an increasingly important component of health systems, but typically come at a high cost that limits widespread access to these important therapies. Biosimilar medicines offer the potential to broaden access to biologic therapies, reducing healthcare inequities and supporting long-term sustainability of healthcare systems. Unlocking the potential of biosimilar medicines relies on development of healthy markets and broad support from all stakeholders. Streamlining regulatory processes to achieve fit-for-purpose requirements in line with scientific and technological progress, stopping abuse of market exclusivity and extensions of intellectual property protections through local legislation or via trade agreements and aligning incentives for payors, prescribers, dispensers and users of biologic medicines are all necessary components of a healthy market.

Specifically, the role of regulatory authorities is critical to establishing robust and sustainable systems for biosimilar competition. A fit-for-purpose framework conducive to the development of quality, safe and effective multisource biologic medicines requires different approaches than for novel biologic medicines. Maintaining consistency in the regulatory approach to evaluating comparability for the biosimilar and for the reference biologic is critical to ensuring rigorous evaluation while minimizing unnecessary components.

A biosimilar development program that maintains the scientific rigor needed to support approval, but allows for a tailored clinical development program, should be adopted by all regulators. This is critical to ensure that patients have access to biosimilar medicines and to have an equitable, sustainable healthcare system. Increasingly, biologic medicines represent the standard of care not only for major diseases impacting large numbers of patients, but also for niche populations suffering from orphan diseases. Ensuring fair competition for biologics with limited patient populations will require a re-thinking of data requirements to support regulatory approval. Current requirements will increase development cost and time to market, which may also significantly reduce the number of developers seeking to bring competition.

Conducting comparative efficacy studies is an expensive and time-consuming effort. If such studies do not contribute useful information, they simply make biosimilar development more expensive and lengthier. The increased cost may deter some potential biosimilar developers, and the extended time to conduct these studies certainly delays approvals which in turn diminishes timely access and cost savings.

As showcased in this policy paper, the role of regulators extends clearly beyond addressing regulatory requirements. Should the development paradigm be adapted to remove the need for comparative efficacy clinical trials, regulators must re-double efforts to inform and educate stakeholders on the demonstrated

⁸ Examples of regulatory authority stakeholder education initiatives include: EMA and European Commission joint stakeholder education materials (<https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview#information-for-patients-and-healthcare-professionals-section> Accessed June 2020)); European regulators paper on biosimilar interchangeability (Kurki et al. *BioDrugs*, 2017 Apr;31(2):83-91, [doi: 10.1007/s40259-017-0210-0](https://doi.org/10.1007/s40259-017-0210-0)); US FDA stakeholder education materials (healthcare providers: <https://www.fda.gov/drugs/biosimilars/health-care-provider-materials>; Patients: <https://www.fda.gov/drugs/biosimilars/patient-materials>)



therapeutic equivalence of biosimilar medicines to mitigate a lack of trust stemming from outdated and scientifically invalid, views of the relevance of clinical data to biosimilar development.

Health system sustainability relies on the establishment of successful biosimilar competition. Stakeholders throughout the value chain – regulatory authorities, payors, healthcare professionals, patients, and others – must ensure that all market elements align to support biosimilar competition to unlock shared benefit. Failure to quickly address barriers to biosimilar medicines will result in increasingly inefficient healthcare spending and limited patient access to life-altering biologic medicines, particularly as therapies evolve to targeted and personalized treatment. Urgent action is needed to ensure continued investment in development of biosimilar medicines, including for non-blockbuster biologic medicines, through health system support for sustained biosimilar competition to benefit tomorrow's patients, as envisioned in the UN Member States Sustainable Development Goals⁹.

⁹ United Nations Sustainable Development Goals 2030 - <https://sustainabledevelopment.un.org/?menu=1300>