Executive summary: Biosimilar Streamlined Development policy paper

Sandoz is proud to lead the way with biosimilars development. We initiated the world's first ever biosimilar development program in 1996 and our growth hormone Omnitrope® was the first biosimilar medicine to receive approval in Europe, Japan, Canada, and the US.

As the world's pioneer in biosimilars, Sandoz plays a crucial role in leading the way towards a sustainable biosimilar market where patients have access to more affordable medicines.

To support these efforts, Sandoz's Global Public Affairs and External Engagement and Regulatory Affairs teams, working with Sandoz's Biopharma Development and a range of subject matter experts throughout the company, have updated the Streamlined Biosimilar Development policy paper, to outline the importance of why and how waiving expensive and time-consuming comparative clinical efficacy studies would provide greater efficiencies and enable biosimilar development for more reference biologics.

Biosimilar development is based on 'comparability studies' that establish biosimilarity to the reference medicine and demonstrate that there are 'no clinically meaningful differences' between the biosimilar and the reference medicine" (1).
By demonstrating high similarity with the reference medicine, the biosimilar can rely on the efficacy and safety experience gained with the reference medicine.

The European Medicines Agency (EMA) was the first agency to set up a biosimilar regulatory pathway in 2004. Biosimilars were entirely a new class of medicines, and their regulatory requirements entailed extensive head-to-head analytical, pre-clinical and clinical comparative studies. This cautionary approach helped gain the trust of prescribers and patients and relied on analytical tools and manufacturing processes used at that time.

Over the years, these guidelines have evolved to reflect rapid advances in biotechnology, analytical sciences and increasing experience of clinical use. For example:

- pre-clinical comparative animal studies are generally no longer required
- Acceptance of clinical pharmacodynamic (PD) biomarker studies instead of larger comparative efficacy studies (5)
- In 2021, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) implemented a biosimilar guidance effectively enabling streamlined biosimilar development for most assets (2).
- In 2022, the WHO Biosimilars Guideline stated 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" (3).
- In 2024, the EMA issued a concept paper for a reflection paper of streamlined development. This is the official start to work on future guidance which may include streamlined development (4).

Advancement in analytical technologies and almost three decades of experience in biosimilars development have shown that **analytical and clinical PK (pharmacokinetic) studies are much more sensitive at finding important differences between a biosimilar and a reference medicine than comparative efficacy studies.** The higher sensitivity of analytical methods can be explained by the fact that such methods can measure the different structural and functional properties directly with high precision and accuracy, whereas the clinical studies results are prone to a much a higher variability and less precision caused by patient variability and confounding factors which are unrelated to the nature of the biologic but which are affecting the efficacy in the individual patients (6).

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With state-of-the-art methods come an opportunity to shift medicines development away from costly, time-consuming, and, because the data is not as accurate as data from analytical and PK studies, ethically questionable, human trials (9).

Streamlined development will enable more biosimilars to be available for more original-brand biologics. This will increase the patient access to biologic treatments by increasing treatment options and affordability.

COMPARATIVE STUDIES		5 Steps - 2004	4 Steps – TODAY	3 Steps - FUTURE
ANALYTICAL		Physiochemical analysis	Physiochemical analysis	Physiochemical analysis
		Functional analysis	Functional analysis	Functional analysis
PRE-CLINICAL		In vivo animal	-	-
CLINICAL	Phase I	Clinical PK/PD	Clinical PK	Clinical PK
	Phase III	Comparative clinical efficacy	Comparative clinical efficacy (conventional endpoint or qualified PD marker)	-

Table 1: *Evolution of the comparative studies divided in analytical, pre-clinical and clinical phases required in 2004, today and by the anticipated future of Streamlined Biosimilar Development*

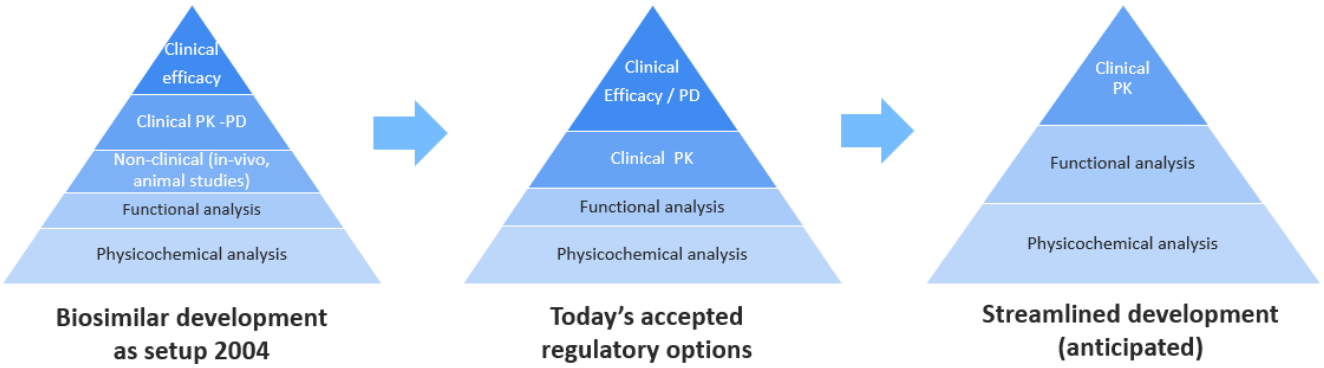

Figure 1: Illustration of the comparative studies required in 2004, today and by the anticipated future of Streamlined Biosimilar Development (right)

Impact: Benefits for patients and other stakeholders

Thanks to the significant experience gained from evaluating a growing number of biosimilars - over 100 approved in Europe and 59 in the US - and considering current advancement in analytical methods, there is a strong case for updating development guidelines to ensure that a streamlined development approach is adopted.

Overall, streamlined biosimilar development using robust scientific tools and advanced analytical methodology will help to encourage the development of more high quality biosimilars. This will expand patient access to high-quality, more affordable biologics without compromising on efficacy and safety.

An optimized biosimilar pathway will bring more efficiency in the development and approval processes and considerable benefits for patients, healthcare systems and healthcare professionals.

Impact on biosimilar development:

1. **Enable biosimilar development to more original-brand biologics:** Currently, about half of the original-brand biologics losing patent exclusivity do not see biosimilar competition because the Phase III clinical efficacy studies are technically or financially not feasible (10). Streamlining will enable biosimilars to those medicines.

2. **Increased efficiency:** Streamlining reduces development timelines (about a year) and costs (about 40% less), enabling more efficient use of scarce resources.
3. **Increased focus on Science**: Health authorities can rely on extensive advanced analytical and clinical pharmacokinetic (PK) studies to ensure biosimilars are safe and effective.

Benefits to Patients, Healthcare Professionals and Healthcare Systems

1. **Increased Access**: Streamlining will enable more biosimilars to be available for more original-brand biologics. This will increase the patient access to biologic treatments by increasing treatment options and affordability.
2. **Affordability**: Increased competition and lower development costs can lead to lower prices for biosimilars, making treatments more affordable for patients.
3. **Enhanced Competition and Innovation**: More biosimilars on the market increase competition, which can drive not only affordability but also innovation that may enable patients to access new treatments earlier due to the resources that are freed up by biosimilars.
4. **Sustainable Healthcare**: Reduced costs and increased access contribute to a more sustainable healthcare system, benefiting both patients and society.

Moreover, eliminating unnecessary clinical studies will reduce patient exposure to clinical studies that are not scientifically justifiable.

Regulators such as MHRA have already worked with the broader healthcare industry with a common goal of policy reform and regulatory harmonization which led to the early adoption of the streamlined approach. Through global adoption of similar principles, a more seamless pathway for large biosimilar portfolios could expand access to millions of additional patients worldwide.

It is critical that industry, regulators and policymakers work together toward global regulatory frameworks in line with the latest scientific knowledge and experience by waiving Comparative Clinical Efficacy trials and harmonizing regulatory requirements across countries.

By streamlining development of biosimilars we can truly drive more timely patient access to high-quality, effective and affordable treatments.

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