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Biosimilars: PrimeVigilance your Partner of Choice for Efficient and Cost-Effective Safety Surveillance

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The rapid development of biosimilars is an undeniable reality; the global biosimilars market **was valued at USD 13.5 billion in 2021** and is expected to grow by 17% at a compound annual growth rate **(CAGR)** to hit **USD 66.2 billion by 2030**. The cost-effectiveness of biosimilars and the rising awareness regarding their availability and effectiveness in the treatment of various highly prevalent disorders are two key factors boosting their global demand.

However, they are intrinsic difficulties in their development as, unlike generics, biosimilars are similar but not identical to the reference innovator products and this similarity poses unique challenges in their manufacturing, clinical development, regulatory approval and pharmacovigilance.

The regulatory authorities have played a crucial role in the adoption of biosimilars by embracing legislative changes facilitating their development and licensure. Furthermore, the rising investment by the key market players in R&D activities is driving innovations in this market. The top sponsors for biosimilar clinical trials include three major pharma companies rather than the more expected 'generic' companies.

The expiry of patents of the earlier biosimilar drugs is offering new opportunities. In the US alone, where the Inflation Reduction Act (IRA 2022) will empower the government to negotiate drug prices for the first time[1] starting in 2023, pharma companies may find themselves grappling with whether to subject their products to price negotiations or alter their patent strategies to let a biosimilar come on the market. There are nearly 40 approved biosimilars approved by the FDA, but only three products are deemed interchangeable (incl. the recently approved inter-changeable product with Lucentis). Even without interchangeability, biosimilars, on average today, cost half as much as the brand name product.

Some key elements to be considered in the development of biosimilars when it comes to safety management:

a. Clinical Development

The basic principle underlying the development of a biosimilar product is comparability with the reference product. Therefore, to be approved, biosimilars have to demonstrate that they are as safe and as effective as the originator reference product (RP) and have the same quality. Biosimilars are evaluated for their comparability with the RP notwithstanding the natural variability inherent to all biological medicines. Biosimilar development relies heavily on comparability studies to establish similarity to the RP. It requires a comprehensive product and process development plus comparative testing at all levels: quality, non-clinical and clinical stages.

[1] Biologics eligible for Medicare negotiation—a process that could take up to two years—must have been on the market for 11 years and not have a biosimilar version on its way to consumers.

Clinical studies are not required to the same extent as for a new active substance due to the well-established profile of the RP. The design of the clinical development program takes into account the nature and the characteristics of the biosimilar and its intended use, as well as how comparable the profile of the biosimilar is with the RP in terms of structure, biological activity and efficacy, safety and immunogenicity profile. Abbreviated clinical trials have helped to ensure that unnecessary testing does not take place and that the development costs are reduced. The clinical comparability exercise usually begins with pharmacokinetic and/or pharmacodynamic studies. As a further step, these studies can be followed by comparative clinical efficacy and safety trial(s) in one or more indications. Besides comparative efficacy, a comparable safety profile in terms of the seriousness and frequency of different side effects must also be demonstrated. Ascertaining comparable immunogenicity profiles between RP and biosimilar is also part of the clinical safety portfolio.

b. Regulatory Review and Approval

In developed markets, simple approval pathways for generic drugs have been in place since the 1980s.

However, these pathways do not apply to biosimilars due to their inherent complexity.

The EU was the first region in the world to have defined the legal framework for the approval of biosimilar products. The concept of a 'similar biological medicinal product' was introduced into EU legislation in 2005, and EMA approved the first biosimilar in 2006, whereas the FDA issued its framework in 2009, and the first biosimilar was approved in 2014.

A review of the regulatory pathways across the largest markets where a biosimilar framework is in place delineates 4 main differentiating parameters, as portrayed in **Table 1** below.

	EUROPEAN MEDICINES AGENCY	U.S. FOOD & DRUG ADMINISTRATION	PMDA	식품의약품안전처
	SCIENCE MEDICINES HEALTH	FDA	独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency	Ministry of Food and Drug Safety
Product specific guidelines available	✓	✗	✗	✓
RP authorized from the same region is required	✗	✓	✓	✗
Interchangeability on the grounds of a switching study	N/A	Randomized switching studies are normally required to prove interchangeability[2]	N/A	N/A
Automatic substitution decisions allowed at pharmacy level	✓	✓	N/A	✗

The outlook of regulators on biosimilar approval appears to be evolving as they gain more exposure over time. For example, the FDA has determined that a switching study was not needed to support the licensure of Cimerli as interchangeable to Lucentis owing to a comprehensive and robust analytical assessment that compared the structural and functional characteristics of Cimerli (ranibizumab-eqrn) to Lucentis (ranibizumab injection) and other clinical safety, immunogenicity and effectiveness data.

In the EMA, the approach is shifting to rely more on the evidence of what the EMA presents as 'physicochemical, functional and pharmacodynamic comparisons' and the results of phase I clinical studies. For example, for biosimilars of low-molecular-weight-heparins, EMA has waived the requirement for pivotal studies. In September 2022, EMA and the Heads of Medicines Agencies (HMA) issued a joint statement confirming that biosimilar medicines approved in the EU are the interchangeable with their reference medicine or with an equivalent biosimilar. While interchangeable use of biosimilars is already practiced in many Member States, this joint position harmonizes the EU approach.

[2] FDA's draft Guidance on Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products leaves room for maneuver, so prior engagement with the FDA in the context of a scientific advice meeting is recommended.

Following Brexit, UK's Medicines and Healthcare products Regulatory Agency's (MHRA) issued **guidance on the licensing of biosimilar products** in May 2021, confirming that in most cases a comparative efficacy trial might not be necessary if a sound scientific rationale is in place. Applicants are encouraged to seek scientific advice to discuss this approach as soon as they have sufficient comparative analytical and functional data to support it. However, final acceptance of this approach would only be considered after the submission of the complete data package. This shift provides biosimilar manufacturers with an opportunity to launch their products in the UK more quickly, and at a lower cost, than in other regions.

c. Post Marketing Safety Monitoring

One of the most important safety concerns relates to biosimilar immunogenicity, the potential for a complex protein like biological to induce an immune response. The immunogenicity of a biosimilar should be closely monitored as the nature and the severity of the immune reactions could be significantly different from those detected with the RP making impossible the simple extrapolation of RP data to their biosimilar counterpart(s). In addition, the long-term exposure to treatment for chronic diseases along with the potential delay between drug intake and the appearance of the immunogenicity reaction can sometimes render the assessment of causality arduous.

The complete immunogenicity profiling of biosimilars cannot be completed during the clinical phases due to the scarcity of enrolled patients and the limited duration of exposure, therefore safety assessment should be continued via post-marketing long-term studies and continued post-marketing pharmacology surveillance. This should be clearly depicted in the submitted Risk Management Plan (RMP) during the marketing application.

The Risk Management Plan (RMP) is a key document for Biosimilars as it provides a detailed set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks, including the assessment of the effectiveness of those interventions. RMP is a complex document since it takes into consideration safety information from the biosimilar and the RP and should include the risk minimization measures that are already in place for the RP.

With a proven track record – preparing over 1500 aggregate reports and RMPs each year – our experts can handle all Aggregate Safety Reporting (ASRs) obligations during clinical development, before the first clock stop and after the first global marketing authorization. Primevigilance has the in-house capability to develop very comprehensive biosimilar RMPs acknowledged by the regulatory agencies as being of high quality and can create common risk management systems between MAHs of RPs and biosimilar products when feasible.

Each safety reaction collected should be carefully evaluated and medically assessed, with the conduct of a close comparison against the safety profile of the reference product to differentiate the safety risks that should be specifically associated with the biosimilar and clearly different from the safety reactions already known and associated to the reference product.

Where PRIMEVIGILANCE can be your Partner of choice for your biosimilar?

Primevigilance end-to-end pharmacovigilance services span **clinical R&D**, **review & registration** and **post-marketing** phases from **ICSR management** to **benefit-risk management**, and from **QPPV & PSMF** to **signal management**.

With over 15 years of experience, PVL offers the unique advantage of a one-stop shop to support all safety requirements associated with the development, regulatory management, and post-marketing safety surveillance of biosimilars. Here are a few services to illustrate how PrimeVigilance can positively impact the safety management of your Biosimilar.

1. Safety Management: a cost-effective operating model

In close partnership with you, Primevigilance can co-develop and review your safety management plan, including business contingency planning. PrimeVigilance has the expertise to set-up a fit-for-purpose safety system and to deploy the appropriate organization and team structure to ensure a high-performing and cost-effective safety monitoring pre-, peri- and post-marketing.

To specifically support biosimilar safety management, PrimeVigilance has a dedicated Biosimilar Business Unit composed of SMEs (Subject Matter Experts) used to articulate optimal PV

operating models using our reliable technology solutions. PrimeVigilance wants to act as a long-term partner for each of their customers, and therefore is able to streamline your PV systems and processes during the expansion of the safety monitoring activities leading to cost and operational efficiencies.

2. Risk Management and Signaling: PrimeVigilance offers a full in-house team with specific biosimilar expertise

Addressing uncertainties in the safety profile at different time points of the biosimilar lifecycle is key given the limited data obtained during the clinical development, largely comprised of phase I and III studies, and the need to compare with the RP. At PrimeVigilance, we recognize that the benefit-risk profile is a dynamic process pre- peri- and post-approval, and in-depth safety monitoring expertise is required.

Our PV experts lead or support your risk management planning in both the pre-approval and post-market settings. PrimeVigilance can navigate you through the development of Risk Minimization Measures (RMM) with an implementation scheme, specific tool recommendations and an evaluation strategy.

3. Benefit-Risk Profile

Through our dedicated signal management, medical monitoring, literature surveillance, medical operations and safety management plan services, our experts 'inform' the benefit-risk profile of your Biosimilar round the clock.

A robust systematic approach to post-approval management of signal detection (SD) is key for biosimilars. It is important to understand the origin of a detected signal and compare it to the signal of the reference product.

Our multidisciplinary team of scientists, in collaboration with PV physicians, have designed, implemented, and overseen compliant signal management processes for over 650 INNs throughout the lifecycle of medicinal products and have identified safety patterns emanated from adverse reactions (AR) data suggesting new safety information.

4. Regulatory Landscape: PrimeVigilance as a unique partner to guide your marketing strategy

Having access to a provider with robust expertise and a global footprint is key in the ever-evolving regulatory environment of biosimilars is beneficial. With its established regulatory department composed of former regulators coupled with the largest PV network, PrimeVigilance can support the development of an optimal regulatory and marketing strategy.

Via Our Local Network and regulatory team, PrimeVigilance can strengthen your negotiations with regulators and HTAs during development and regulatory review.

In addition, our Regulatory Intelligence can monitor the expected changes in safety reporting requirements in different regions or specific countries; allowing you to receive possible modifications impacting the biosimilar development or post-marketing requirements ahead of time.

5. Quality is Paramount: PrimeVigilance, a guarantee for successful inspections outcomes

Quality Assurance PrimeVigilance offers extensive support to customers ahead of audits or inspections, ensuring an optimal outcome. Having supported over 240 regulatory authority inspections successfully worldwide between 2005-2021, our QA team can guarantee that you will always be inspection ready. Through our QbD approach based on data integrity, scientific evaluation of quality risks and effective communication, we prepare our clients for routine Good Pharmacovigilance Practices (GVP) inspections, as well as 'for cause' pharmacovigilance inspections by regulatory authorities and third-party vendors/partners. We provide post-inspection assistance and prepare **SMART** (**S**pecific, **M**easurable, **A**chievable, **R**ealistic, **T**ime Driven) responses.

To learn more about PrimeVigilance's expertise in delivering high quality, fully compliant global life cycle management solutions, contact us at:
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