

# **Biosimilars- An opportunity to update the Product Information of biological drugs regarding their immunogenicity**

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**Running Heading:** Biosimilars as an opportunity to update the Product Information of biological drugs

One of the greatest theoretical clinical concerns regarding the development of biosimilars has been that post-translational protein modifications, even while antigen binding remains essentially unaltered, might result in detrimental immunogenicity. We recently demonstrated [1] that the Summary of Product Characteristics (SmPCs) of biological drugs, approved by the European Medicines Agency (EMA), are very heterogeneous regarding the issues related to immunogenicity that are addressed within these documents. A complementary analysis, using the methodology advanced in [1], to the EMA's documents "Procedural steps taken and scientific information after the authorisation" shows that 57% (30/69) of the biological drugs that have been authorized prior to 2012 did not update their SmPC at least once when it comes to information related to unwanted immunogenicity. These are surprising results given the advancements that have been seen in the field of immunogenicity assessment [2], namely in the development of more

sensitive and drug tolerant assays. These recent assays detect Anti-Drug Antibodies (ADAs) in a significantly greater proportion of patients and are being commonly employed in Bioequivalence studies in order to detect, if present, small differences between Biosimilars and the Reference Product. On the other hand, immunogenicity results reported in the SmPCs of these Reference Products are usually based on assays developed and validated 10-15 years ago. Given that the immunogenicity rates reported by SmPCs influence the perception of the medical community about how often the development of an immunogenic response against a biological drug occurs, we wonder if the SmPCs of older drugs should not be updated, when data is available, to also reflect the immunogenicity rates that are being detected with these newer assays. Thus, a perfect opportunity to update the information in some of these SmPCs arises from the approval of biosimilars.

According to European guidelines, a biosimilar is defined as a biological medicine that is a highly similar version of an already established biological drug (reference product) in the European Economic Area. Therefore, getting approval into the European Market requires that these products demonstrate a high degree of similarity (in terms of quality, biological and medical properties) between themselves and their counterparts [3]. This assessment includes head to head clinical studies that compare a biosimilar's immunogenicity profile to its' Reference Product and this analysis is extremely relevant due to the low predictability that non-clinical models confer regarding the unwanted immunogenicity of biological drugs.

The Biosimilar Medicinal Products Working Party (BMWP) reported in 2012 three different options for reporting of bioequivalence data in the SmPCs of biosimilar drugs. These options ranged from not including any information at all up to only reporting the bioequivalence data supporting EMA's assessment [4]. The decision that came from this discussion was that a Marketing Authorisation Holder must develop a document identical (with the exception of using the International Nonproprietary Name of the active substance instead of the tradename of the reference product [5]) to the SmPC of the reference product, thus excluding any bioequivalence data from the SmPCs and include it exclusively in the product's European Public Assessment Report (EPAR). We argue that this is an inadequate strategy given the low proportions of Healthcare Professionals that use EPARs as a source of information [6]. Additionally, we would argue that excluding information about the bioequivalence studies in the SmPCs increases the

likelihood of misunderstandings and unreasonable fears by some members of the medical community. On the other hand, the regulators' stance that different SmPCs between products with a similar active substance could lead to misunderstandings is also sensible [7]. Therefore, considering both sides of the argument, we propose the idea that both the SmPCs of the reference product and of the biosimilar product should include data from the bioequivalence studies, specifically the data related to the immunogenicity.

From the reference products' perspective, we argue that this update is necessary given that most of these drugs have been on the market for over 10 years. During this period, an increasingly higher number of improvements regarding the assessment of immunogenicity have occurred but many SmPCs include data mostly obtained during the drug's pivotal clinical trials [8], thus possibly underestimating the immunogenic potential of some products [9]. Consequently, the inclusion of immunogenicity data from bioequivalence studies, assessed with new methodologies, could be an excellent opportunity to update these drugs' SmPCs in order to provide a better sense of amplitude about the detected incidence of ADAs.

While the possibility of including information in the SmPCs of both the Reference Product and of the biosimilar drugs had not been considered by the BMWP, this is not a novel solution. Common updates, regarding immunogenicity, to SmPCs of different biological products that contain the same or closely related active substance can be seen in several situations identified in Table 1. Examples of these include the updates A31/0134 and A31/0178 for moroctocog alfa (ReFacto AF) and octocog alfa (Helixate NexGen) respectively [13, 14] or the update IB/0002/G for epoetin theta (Biopoin and Eporatio) [15, 16].

From the biosimilars' perspective, we argue that this update is necessary because issues such as immunogenicity [10], switching/interchangeability [11, 12] and extrapolation of indications [7] have been raised throughout the years. Inclusion of immunogenicity data collected during the bioequivalence studies can help clarify some of these issues in a document that is regularly used by HCPs. Additionally, by reporting data that supports the decision to approve a biosimilar into the European Market might help invalidate the perception that the evidence supporting this decision is insufficient [7], while excluding data from bioequivalence studies foments this perception.

Table 1- Common updates to the immunogenicity information addressed by SmPCs of different biological products

Scope	Active Substance	Commercial Name	Application Number
The PRAC was requested to assess the potential impact of the results of the SIPPET study (which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines), and to issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.	Moroctocog Alfa	ReFacto AF	A31/0134
	Octocog Alfa	Advate	A31/0078
		Helixate NexGen	A31/0178
		Kogenate Bayer	A31/0185
The MAH applied for a type II variation, upon request from the CHMP following a class review of recombinant Factor VIII medicinal products, to update section 4.4 of the SPC to include a warning on cases of inhibitors (...)	Octocog Alfa	Helixate NexGen	II/0058
		Kogenate Bayer	II/0058
		Advate	II/0022
To update Section 4.4 "Special Warnings and Precautions of Use" of the SmPC with the following wording: A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. (...)	Epoetin Theta	Biopoin	IB/0002/G
		Eporatio	IB/0002/G
The MAH has updated section 4.4 'Special Warnings and precautions for use' of the SPC to include a cross-reference to antibody formation already present in section 4.8 'Undesirable effects', as previously requested by the CHMP.	Insulin Glargine	Lantus	II/0041
		Toujeo	II/0027

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