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LETTER TO THE EDITOR

Author's Reply to Borg et al. Comment on: "EU's New Pharmacovigilance Legislation: Considerations for Biosimilars"

Begoña Calvo

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The article "EU's New Pharmacovigilance Legislation: Considerations for Biosimilars" has mainly focused on the new European Pharmacovigilance normative, which, in general, also applies to similar biological medicinal products [1]. Specific implications of this legal rule for biosimilars have been succinctly addressed.

The Borg et al.'s comment addresses issues that could be discussed more thoroughly [2]. In such a case a broader article specifically devoted to biosimilars pharmacovigilance would be needed.

The main issues of the comment, along with a brief response from one co-author of the article, appear below:

(1) *Do small differences* (*large ones would not be accepted*) *impact the safety profile of the biosimilar beyond of what can be seen from clinical trial data?*

A biosimilar can show small differences compared to the reference product. An effect of these differences on efficacy and/or safety can be expected or can not be rejected, in spite of the state of the art physico-chemical and biological assays. In such cases, additional non-clinical and/or clinical studies will be necessary, as well as a specific post-authorization follow-up. The same applies to an innovative biopharmaceutical product if any changes are made in the manufacturing process [3].

The need, extent and nature of clinical studies will be scheduled on a case-by-case basis taking into account various factors that may be related to risks, such as:

- The nature and extent of differences demonstrated by the physico-chemical and quality-related biological characterisation, including product-related substances, impurity profile, stability and excipients.
- Previous experience, e.g., immunogenicity, safety. Experience with the reference product or with other products within the same class can be relevant.

(2) *Are there differences in the impurity profile* (*a biological is more than the active substance*), *and is there a higher immunogenicity*?

Even if the efficacy is shown to be comparable to the reference product, the biosimilar may exhibit a difference in the safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Pre-licensing safety data should be obtained in a number of patients sufficient to compare the adverse effect profiles of the biosimilar and reference product. Further post-licensing studies may occasionally be needed, e.g. pharmacoepidemiological studies. Applicants should in their risk-management plan (RMP) not only include the adverse events incidence, but also possible differences in clinical presentation (duration, severity and seriousness, reversibility, response to treatment etc.).

Specific safety endpoints should be selected, taking into account both the typical safety findings known for this product and/or this product class and other potential safety findings, which can be deduced from the action mechanism. Since unexpected safety findings might occur, applicants should set up methods in the study protocols aiming at the detection of both known and unknown safety issues [4].

Product-related factors influencing the immunogenicity of biotechnology-derived therapeutic proteins include the nature of the active substance (structural homology,

B. Calvo (✉)
Pharmaceutical Technology Department, Faculty of Pharmacy, University of the Basque Country, P. Universidad, 7, 01006 Vitoria-Gasteiz, Spain
e-mail: b.calvo@ehu.es

post-translational modifications), modification of the native protein, product- and process related impurities (e.g. breakdown products, aggregates and host cell proteins, lipids, etc.), and formulation. Biotechnology-derived analogs to human endogenous proteins may trigger an immune response due, for example, to changes to the protein structure as a result of post-translational modifications. Glycosylation is a frequent post-translational modification of biotechnology-derived therapeutic proteins. These modifications may differ in the number and position of glycosylation sites as well as sequence, chain length and branching of the attached oligosaccharide. Therefore, when the same protein is manufactured under different conditions, as in the case of biosimilars, there might be changes in the pattern of post-translational modifications and the immunogenic potential of the protein.

Unwanted immunogenicity can occur at a level, which will not be detected by such studies when conducted at a pre-approval stage, due to the small number of patients participating in the study. Therefore, it is often necessary to continue assessment of unwanted immunogenicity and its clinical significance post-approval, usually as part of pharmacovigilance surveillance.

The extent of immunogenicity studies, if required, should be based on risk analysis and should be proportional to the identified risks, taking into consideration the nature of the observed difference, the potential clinical impact, and knowledge gained with the reference product. Likewise, RMP should discuss any rare serious adverse events associated with the specific class of biopharmaceuticals.

(3) *What about the need for post-authorisation data for indications not specifically studied* (*i.e., indications authorised for the reference product but not specifically studied for the biosimilar which were "extrapolated", based on the entirety of data from the biosimilar comparability exercise*)?

In the event that the biosimilar is used for indications not specifically studied in the comparability exercise, the impact of possible differences on post-authorisation efficacy and/or safety should be analyzed. Marketing authorisation holders may have post-approval commitments defined in the risk-management plan, to characterize safety profile more fully, in order to establish long-term safety.

(4) *It will be important to distinguish if a particular adverse drug reaction comes from the biosimilar itself* (*thus potentially impacting its benefit/risk profile*), *or if it is a result of the switching process from the originator biological to the biosimilar…*

The potential substitution at the pharmacy level of the innovator product by the biosimilar has important implications for pharmacovigilance, including assessment of efficacy and safety, and ensuring traceability. The possibility of switching biosimilars emphasizes the need to accurately identify which product was used. Such switching may introduce challenges for tracking the product a patient has received, thereby making attribution of adverse events difficult. This is particularly important if the immunogenicity profile of the product evolves over time [5].

Finally, we must emphasize that upon demonstrating its similarity through the comparability exercise, a biosimilar is as safe as the reference product, provided that the requirements of pharmacovigilance legislation are met. Thereby, the guidelines state that 'clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment'. Furthermore, any safety monitoring required for either the reference product or the individual products within the product class should be taken into consideration in the biosimilar RMP [6].

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