Drug Saf (2014) 37:123–124
DOI 10.1007/s40264-013-0128-5

LETTER TO THE EDITOR

Comment On: "EU's New Pharmacovigilance Legislation: Considerations for Biosimilars"

John Joseph Borg · Anthony Serracino-Inglott · Lilian M. Azzopardi · Christian K. Schneider

Published online: 13 December 2013

In an article recently published in Drug Safety, Calvo and Zuñiga review the new EU legislation on pharmacovigilance and its impact on biosimilars [1]. The authors discuss that the new legislation clarifies the marketing authorisation holders' responsibilities for continuously monitoring the safety of medicinal products for human use, and that on a number of issues the new legislation introduces changes that strengthen the EU pharmacovigilance system. Biosimilars can be developed for any biological medicinal product [2]; in practice, this is carried out for well-characterized biologicals. The more complex the reference product is, technical limitations (chemistry, manufacturing, and control, as well as pharmacodynamic effects) could prevent the applicant from proving biosimilarity of the new developed product. However, there are challenges that are rarely discussed from a pharmacovigilance perspective as they deal with issues of a pre-authorisation development, but which affect the pharmacovigilance plan that needs to be developed for market surveillance of the biosimilar medicinal product. During the assessment of a biosimilar marketing authorisation application, EU regulators are challenged on where the boundaries lie of what are considered acceptable 'minor differences' which still allow the establishment of 'biosimilarity' of a biosimilar candidate. The more complex the medicinal product is the more difficult it is to characterize differences. While differences in primary structure are not within the definition of a biosimilar [3], due consideration of minor differences in higher order structure, glycosylation, and product- and process-related impurities need to be made during the evaluation process in order to establish that a biosimilar candidate is a 'true' biosimilar (larger differences would not be in line with the biosimilar principles and thus not be acceptable) [4]. The extent of similarity will proportionally define what is required for a biosimilar regarding the risk-management plan (RMP).

To date we could assume that it is more challenging to develop biosimilars for blood- or plasma-derived products, gene/cell therapy products and advanced therapy medicinal products due to their complexity. Inherently, there are cons to the biosimilar approach for each individual biological medicinal product and these should be evaluated on a case-by-case scenario during the pre-clinical development phase. Such issues need to be fed to the pharmacovigilance section of the dossier to prepare the RMP required for a marketing authorisation application.

Every biological is unique, and the developer of a biosimilar candidate has to design their own manufacturing process for their product. While it is true that small structural changes (such as those arising during the manufacture of a biosimilar even in the same expression system as the reference product) can have significant functional consequences, such differences will usually be detected in functional assays and in a clinical study 'model' which is sensitive enough to establish biosimilarity. Only biosimilar candidates that are highly similar to their reference product

J. J. Borg (✉) · A. Serracino-Inglott
Medicines Authority, 203 Level 3, Rue D'Argens, Gzira GZR 1368, Malta
e-mail: john-joseph.borg@gov.mt

A. Serracino-Inglott · L. M. Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

C. K. Schneider
Danish Health and Medicines Authority, Copenhagen, Denmark

C. K. Schneider
Twincore Centre for Experimental and Clinical Infection Research, Hannover, Germany

will jump the hurdle of marketing authorisation in the EU and thus become 'true' biosimilars. The implications of an own manufacturing process newly established for a biosimilar in line with current International Conference on Harmonisation (ICH) guidelines, and its implications on the safety/efficacy of the biosimilar product, must be fully discussed and justified a priori to licensure. The efficacy and safety of monoclonal antibodies, as an example of a popular class of biosimilar candidates, are in most cases related to the high specificity of epitope recognition, which makes performing non-clinical studies in animals more difficult (or even unfeasible), thus putting more burden on in vitro physicochemical and functional tests and the pivotal clinical study. This raises a number of issues: do small differences (large ones would not be accepted) impact the safety profile of the biosimilar beyond what can be seen from clinical trial data? Are there differences in the impurity profile (a biological is more than the active substance), and is there a higher immunogenicity? 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)? It is therefore inherent that applicants for a biosimilar candidate present an RMP in accordance with specific current EU legislation and pharmacovigilance guidelines, and also in line with both product-specific development guidelines and the biosimilar principles. It must be emphasised that the RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product (since it refers to it). If necessary, the RMP should also be based on overall evaluation and safety in indications authorised for the reference product that are claimed to be based on extrapolation (extrapolation may not necessarily trigger automatic RMP activities; it depends on how conclusive the overall dataset on close similarity was). Rare serious adverse events known to be associated with specific classes, such as for low-molecular weight heparin (e.g. heparin-induced thrombocytopenia type II [HIT II], heparin-induced thrombocytopenia thrombosis [HITT], anaphylactoid and anaphylactic reactions) should specifically be discussed in the RMP, even if they were not detected in clinical trials.

Overall, it is our opinion that the new EU pharmacovigilance legislation does not (and should not) introduce specific obligations for biosimilar products over and above those of biological medicinal products. The idea of 'proportionality' should prevail—for example, many issues as regards 'unknown risks' will, at the time the biosimilar is authorised, already have been solved with data from post-authorisation follow-up from the reference medicinal product. Regulators will be challenged with post-authorisation adverse drug reaction reports when biosimilars are more widely used. 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 (thus not necessarily impacting on the benefit/risk profile per se)—short-sighted assessment may lead to the wrong conclusion that an otherwise safe biosimilar is an unsafe drug.

Acknowledgments The authors wish to thank Amy Tanti for her comments during the preparation of this letter.

Disclaimer The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties, any national competent authority, or any University.

Funding Sources of support: John Joseph Borg and Christian K. Schneider are full-time employees of the Malta Medicines Authority and the Danish Medicines Agency, respectively. Anthony Serracino-Inglott and Lilian M. Azzopardi are full-time employees of the University of Malta. The institutions the authors are affiliated with had no role in the preparation of the letter or the decision to submit it for publication.

Conflict of interest All authors (John Joseph Borg, Anthony Serracino-Inglott, Lilian M. Azzopardi and Christian K. Schneider) have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: they had no financial support from any institution or third party; no financial relationships with any organisation that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

References

1. Calvo B, Zuñiga L. EU's new pharmacovigilance legislation: considerations for biosimilars. Drug Saf. 2013;. doi:10.1007/s40264-013-0121-z.
2. European Medicines Agency. Draft guideline on similar biological medicinal products CHMP/437/04 Rev. 1. pp. 1–6, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf. Accessed 6 Nov 2013.
3. European Medicines Agency. Draft guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMA/CHMP/BWP/247713/2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127960.pdf. Accessed 6 Nov 2013.
4. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, Heim HK, Heinonen E, Ho K, Thorpe R, Vleminckx C, Wadhwa M, Schneider CK. Biosimilars: why terminology matters. Nat Biotechnol. 2011;29(8):690–3.