ESMO Open
Cancer Horizons

The ESMO position paper on biosimilars in oncology: enhancing the provision of accurate education and information

Martin Schiestl,[1] Andriy Krendyukov[2]

To cite: Schiestl M, Krendyukov A. The ESMO position paper on biosimilars in oncology: enhancing the provision of accurate education and information. *ESMO Open* 2017;**2**:e000245. doi:10.1136/esmoopen-2017-000245

Received 10 July 2017
Accepted 11 July 2017

[1]Sandoz GmbH, Kundl, Austria
[2]Sandoz Biopharmaceuticals,Hexal AG, Holzkirchen, Germany

Correspondence to
Dr Andriy Krendyukov; andriy.krendyukov@sandoz.com

The recent ESMO position paper on biosimilars in oncology[1] was timely, given the rapidly increasing range of biologic medicines and the potential to develop biosimilar medicines in this area. As the position paper clearly states, biosimilar medicines can positively impact the financial sustainability of healthcare systems around the world.[1] The paper also correctly highlights the importance of providing accurate information to all stakeholders involved. This is essential in order to avoid misunderstanding and misconceptions about biosimilar medicines.

Biologic medicines, whether reference biologics or biosimilars, are recognised as being much more complex than traditional, chemically-synthesised drugs. A biosimilar, as defined by the EMA, is a biologic medicine that is similar to another biologic medicine that has already been authorised for use.[2] A science-based regulatory framework has been established in the European Union (EU) since 2005 to ensure the development and approval of high-quality biosimilars; this framework is regularly reviewed and updated.[3–5] The requirements for biosimilar development and approval are based on those that are in place for any biologic medicine; the manufacturer is required to demonstrate similarity to the reference medicine in terms of safety, efficacy and quality. This contrasts with the requirements for approval of generic versions of chemically synthesised, small-molecule drugs, which typically only require demonstration of identical structure and pharmacological bioequivalence to gain approval.[1]

Extrapolation is one area of the biosimilar concept that is commonly misunderstood by practising healthcare professionals. It is defined as the authorisation of a biosimilar for clinical indications of the reference biologic without the need to conduct clinical trials in those indications. The regulatory framework for the development of biosimilar draws on scientific principles that have been employed in the pharmaceutical industry for decades.[6 7] Processes for manufacturing biologic medicines are frequently changed, for example, to enable scaling-up of the production, to improve its efficiency or to enable equipment to be updated or replaced.[8] Indeed, it is reasonable to conclude that current versions of many biologic medicines are no longer identical to the versions that first received marketing authorisation.[7] Pharmaceutical regulators therefore developed 'the comparability concept' as a mechanism to establish whether premanufacturing and postmanufacturing change biologic medicines are sufficiently similar to allow continued authorisation without the need for a new/repeated clinical trial programme. This requires that existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact on safety or efficacy of the drug product.[9]

The same scientific principles that apply to the comparability exercise described above are also applied to the comparability exercise for demonstrating biosimilarity, and from a scientific and regulatory perspective, the active substance of a biosimilar is just another version of the active substance of the reference biologic medicine.[7 10] In other words, extrapolation is based on the demonstrated level of sameness from molecule to molecule and not from indication to indication.

Another key element of the biosimilar concept is that confirmatory clinical phase III trials are typically conducted in a sensitive indication (indication in which any potential difference between the reference and biosimilar medicine is likely to be observed). As the first biosimilar medicines in Europe were approved a decade ago, there are now several good examples that confirm the validity of

extrapolation of indications for biosimilars.[7] Confirmatory studies for biosimilar filgrastims were conducted in patients with breast cancer who had chemotherapy-induced neutropenia, while other indications were granted based on extrapolation. Subsequent postmarketing and real-world studies have confirmed the safety and efficacy of these biosimilars in all approved indications and different tumour types, including stem cell mobilisation.[7] For example, recently published real-world evidence data with biosimilar filgrastim in patients suffering from diffuse large B-cell lymphoma confirmed once more its safety and efficacy in oncological practice.[11] Another example is the biosimilar epoetins. For these medicines, chronic kidney disease-related anaemia is recognised as the most sensitive indication since these patients have a deficiency in endogenous erythropoietin and a responsive bone marrow (as compared with patients with cancer who are receiving chemotherapy). Again, postmarketing and real-world studies have not exposed any concerns with these biosimilar medicines in extrapolated indications.[7]

It is also important to highlight a recent article that was published after the ESMO position paper emerged. The ESMO position paper includes a section on interchangeability, switching and automatic substitution.[1] The paper correctly states that decisions on the interchangeability and substitution of medicines are the responsibility of EU member states. It also notes (correctly at the time of its publication) that the EMA had not provided any recommendations on interchangeability.[1] Since then, however, a publication by well-regarded regulatory experts has provided a European perspective on this area.[10] The article defines interchangeability as 'the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of, the prescriber'. Substitution is defined as 'the decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient'.[10] Following a critical assessment of the potential risk of switching from reference biologic medicine to a corresponding biosimilar medicine, the authors conclude that switching between a reference medicine and a biosimilar version (by definition approved in accordance with European legislation) is not expected to trigger or enhance immunogenicity.[10] They go on to say that, based on existing knowledge, 'it is unlikely and very difficult to substantiate that two products, comparable on a population level, would have different safety or efficacy in individual patients upon a switch'.

It is encouraging to see ESMO take an initial position on the role of biosimilars in oncology. Such societies have an important role to play in providing accurate information, as well as education, to all stakeholders. They will also be pivotal in providing future guidance and potential follow-up positioning on key issues such as extrapolation and interchangeability/substitution in clinical oncology.

Contributors Both authors contributed and approved the submitted editorial.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Tabernero J, Vyas M, Giuliani R, *et al*. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 2017;1:e000142.
2. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products), 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf (accessed 27 Jun 2017).
3. European Medicines Agency. Guideline on similar biological medicinal products, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed 27 Jun 2017).
4. European Medicines Agency/European Commission. Biosimilars in the EU. Information for healthcare professionals, 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (accessed 27 Jun 2017).
5 European Medicines Agency . Guideline on similar biological medicinal productscontaining biotechnology-derived proteins as activesubstance: non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf.
6 Weise M, Bielsky MC, De Smet K, *et al*. Biosimilars: what clinicians should know. *Blood* 2012;120:5111–7.
7 Weise M, Kurki P, Wolff-Holz E, *et al*. Biosimilars: the science of extrapolation. *Blood* 2014;124:3191–6.
8 McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther* 2012;91:405–17.
9 ICH. Q5E guideline on 'Comparability of biotechnological/biological products subject to changes in their manufacturing process', 2004. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed 28 Jun 2017).
10 Kurki P, van Aerts L, Wolff-Holz E, *et al*. Interchangeability of Biosimilars: A European Perspective. *BioDrugs* 2017;31:83–91.
11 Gascon P, Krendyukov A, Höbel N, *et al*. Treatment patterns and outcomes in the DLBCL cohort of a study (MONITOR-GCSF) assessing biosimilar filgrastim for prophylaxis of chemotherapy-induced/febrile neutropenia. *Hematol Oncol* 2017;35:351.