

Biosimilars for Healthcare Professionals

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Biosimilars versus 'biobetters'—a regulator's perspective

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The attractiveness of the biosimilar regulatory pathway is threatened by so-called biobetters. This paper provides definitions and an overview of recent developments.

Keywords: Biobetter, biosimilar, competition, interchangeability, regulatory pathway

Concerning the biosimilar landscape, the European Medicines Agency (EMA) was among the first institutions to offer a legal basis and regulatory guidance for biosimilar development. Since 2004, the available guidance documents have flourished and evolved to ensure high standard biosimilar medicines for patients throughout the European Union (EU). Biosimilar medicines seemed to be the ideal solution for healthcare representatives in fear that a growing number of highly expensive biologicals would sooner or later crash their systems and leave the costs of high-end treatment to the patient. Additionally, biosimilars, like generics, were considered innovation drivers, urging developers to focus on novel targets rather than stick with established top sellers.

After the first guideline was in place, the new concept was taken up with varying speed and varying success. While some markets were quick on uptake of biosimilars, other countries seemed more hesitant to incorporate the novel concept into daily practice [1]. It took time, but in 2013, biosimilar development started to gain momentum, with the positive CHMP (Committee for Medicinal Products for Human Use) opinion to Celltrion's Remsima (infliximab) – the first biosimilar monoclonal antibody – developed from a South Korean Company. Even more encouragingly, within the EU, Remsima was able to obtain all major indications of originator Remicade by extrapolation. To date, 19 biosimilar medicines have a valid marketing authorization, and many more are waiting in the pipelines. More and more European markets jumped on the biosimilar

bandwagon resulting in Italy overtaking Germany as the biggest European biosimilar market [1]. Biosimilars can be considered a success story – yet they are in fierce competition with a different player, which is from a European regulatory perspective, no player at all – the 'biobetters'.

The term 'biobetter' was presumably invented by Mr GV Prasad, CEO of Dr Reddy's Laboratories, at a bio-investor's conference in Mumbai, India, in 2007 and has been excessively used ever since, possibly to a degree, where there is no unified definition for this marketing term [2].

While biosimilars, as the term suggests, aim to establish similarity to a known biological, biobetters seek superiority in one or various aspects of their clinical profile. While working against the same target protein, biobetters include structural changes, bi-functional targeting (with or without a biosimilar core) or an improved formulation that may result in an expected improvement in safety and/or efficacy [3].

Sharing the same target and being an improved version of a known biological sets biobetters apart from so-called 'me-too biologicals', which, without being structurally based on each other, share the same target, e.g. anti-TNF α monoclonal antibodies.

An interesting example of a biobetter, which could possibly reduce the impact of potential biosimilar candidates is the development of Roche's obinutuzumab (Gazyvara), an anti-CD20 monoclonal antibody, which has shown superior efficacy in the treatment of chronic lymphocytic leukaemia

(CLL) compared to its 'originator' rituximab (MabThera, Roche). Gazyvara gained EU marketing authorization for previously untreated CLL in 2014 – before biosimilar candidates of rituximab managed to finish their development programmes. However, it remains to be proven if Gazyvara can demonstrate a more favourable benefit/risk ratio than rituximab in other indications than CLL and to what extent it will replace MabThera, as well as putative biosimilar rituximabs, in the future.

While no special regulatory pathway for biobetters exists, a biobetter will always be treated as a product with new active substance from a regulatory perspective, some 'short cuts' might remain for biobetter developers. Knowing your target can reduce R & D costs, prior related drugs may help with choices of biomarkers and safety monitoring will most likely focus on known side effects of the already established target pathway. Furthermore, if a biobetter gains a marketing authorization, this may lead to market exclusivity, even if no patent protection will be issued. Sometimes, biobetter development is even used as a defence strategy of originator companies, to protect their market niche against possible biosimilar candidates via line extensions, as in the case of a subcutaneous formulation of Roche's trastuzumab, which gained positive marketing authorization in 2013 shortly before Roche's Herceptin (intravenous trastuzumab) patent expired in 2014.

Apart from the lack of new targets, the rise of biobetters can partly be attributed to certain regulatory pitfalls in the European biosimilar regulatory framework. For instance, the sensitive issue of interchangeability has, to date, not been addressed by EMA because interchangeability is tightly connected to substitution which is a national issue. In the absence of national legislation and guidelines, the decision if and under which circumstances interchangeability could be established remains with individual doctors, especially in the context of hospital tendering processes [4]. Hence, it remains unclear whether, like generic drugs, biosimilars will be prescribed interchangeably with their originator in the near future.

To keep the biosimilar concept attractive for companies, regulatory guidance needs

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to evolve to more thoroughly address most urging regulatory questions in order to ease global developments. In line with this, the concept of extrapolation of indication has further been elaborated in a recent article issued by members of EMA's Biosimilar Medicinal Products Working Party, specifying circumstances under which extrapolation to all originator's indications can be possible [5]. Furthermore, in 2013 the new draft of EMA's overarching biosimilar guideline opened the door to waiving clinical studies in biosimilar development under specific circumstances, e.g. for structurally more simple biological medicinal products, which in the future will have to be further specified to help companies in planning their biosimilar development programmes [6].

In conclusion, in a highly regulated market, such as the EU, the biosimilar concept stands a fair chance to continue

posing an attractive regulatory pathway for drug developers, compared to developing 'biobetters' via a full application, thereby fulfilling the rising need for cheaper biological medicinal products. Regulatory guidance will further have to evolve, to keep biosimilars competitive against biobetters and to avoid pitfalls in their development.

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