ABSTRACTED SCIENTIFIC CONTENT

Biosimilar monoclonal antibodies – time for a regulatory rethink

The approval of biosimilars in the European Union (EU) is governed by the EU biosimilar framework released in 2004. But new arrivals on the biosimilar stage – monoclonal antibodies – are forcing regulatory authorities to reconsider what constitutes a biosimilar, writes Dr Ebbers and co-authors [1].

Many monoclonal antibodies (mAbs) will lose patent protection in the next few years. The patent of the cancer mAb bevacizumab (Avastin), for example, will expire in the US in 2017 and in the EU in 2019, creating a space in the market for lucrative (but relatively low cost) biosimilar versions. Under the EU biosimilar framework, comparative, analytical, preclinical and clinical studies should demonstrate comparable quality, safety and efficacy to a product authorized in the EU before a product is approved. But monoclonal antibodies are considerably more complex than currently approved biosimilars such as epoetins and recombinant human growth hormones.

Post-translational modifications

The primary sequence of biosimilar antibodies should be identical to the reference product, and the product attributes should be comparable for biosimilars. But the primary sequence will miss differences in post-translational modifications that can affect the immunogenic potential of a product, and differences in production can lead to differences in effector functions, pharmacokinetics (PK) and pharmacodynamics (PD). For this reason, an EU guideline outlining the approval criteria for biosimilar mAbs has been released, outlining a case-by-case approach to the comparability exercise.

Dr Ebbers and co-authors have reviewed the possibilities and challenges of a comparability exercise for the cancer mAb bevacizumab, focussing their review on *in vitro*, *in vivo* and clinical studies.

Post authorization

The findings reveal that the trial sizes needed to demonstrate biosimilarity with this mAb would be impractical for some of the relatively uncommon cancers it is used to treat. Also, there is a dearth of appropriate clinical endpoints associated with bevacizumab, raising the possibility of authorizing biosimilars not only on the basis of extensive *in vitro* and *in vivo* studies, comparable PK, immunogenicity and clinical efficacy, but also on sufficient long-term efficacy data collected post authorization.

The authors show that anticancer mAbs such as bevacizumab could force regulatory authorities to reconsider the objective of the comparability exercise. European legislation currently requires products to 'demonstrate biosimilarity', but Dr Ebbers argues that it might be best to 'exclude excessive dissimilarity'.

Demonstrating that two products are similar under these constraints is 'conceptually challenging' writes Dr Ebbers, and there is clearly no one-size-fits-all when it comes to complicated products like bevacizumab. Authorizing cancer mAb biosimilars at realistic costs will require 'novel approaches to the clinical development programme,' he concludes.

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Reference

1. Ebbers HC, van Meer PJ, Moors EH, Mantel-Teeuwisse AK, Leufkens HG, Schellekens H. Measures of biosimilarity in monoclonal antibodies in oncology: the case of bevacizumab. Drug Discov Today. 2013 Sep;18(17-18):872-9.

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