European Regulators Update Guideline on Protein Biosimilars

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The European Medicines Agency ("EMEA") has provided updated guidance on obtaining protein biosimilar approvals. This document is called "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev1). This follows circulation of a draft to industry for comment in 2013. The new guideline is effective July 1, 2015.

The document provides the non-clinical and clinical requirements for a biosimilar to be approved for marketing in Europe. The guidance is significant because other regulators often look to the EMEA criteria - Europe is a leader in developing criteria for biosimilar approvals. The revised guidance emphasizes conducting non-clinical and clinical studies in a stepwise manner and outlines recommended approaches.

The non-clinical requirements include analytical studies and pharmaco-toxicological studies. Analytical studies, such as assessing target binding and functional effects, should be comparative, showing similarity to the reference (brand name) drug. The assays and data required will depend on the product class. The studies must show that in vitro assays are representative/predictive of clinical effects.

The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, and efficacy studies. It also addresses clinical safety. The clinical portion of the revision addresses, for example, study design, choice of patient population and endpoints in efficacy trials. Safety is also addressed, including risk management, pharmacovigilance and immunogenicity study design (the EMEA has a separate guidance document on immunogenicity studies).

Providing data to support extrapolation of safety and efficacy is also addressed, which is a particular point of interest. The approved reference product may have multiple therapeutic indications. Biosimilar companies typically want to demonstrate biosimilarity in one indication and extrapolate the clinical data to other indications. For example, in September 2013, the EMEA approved Europe's first biosimilar antibody. The drug was Inflectra which is a biosimilar of Remicade (infliximab), an anti-TNF-α antibody to treat autoimmune diseases. Remicade sales in Europe were over US$2 billion in 2012. The EMEA was willing to fully extrapolate from the limited clinical data set in the Inflectra drug submission to all the other approved previously approved indications for the reference product. As a result, Inflectra was approved in Europe for the treatment of inflammatory conditions including rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis. The situation was different in Canada, where the regulator, Health Canada, did not permit extrapolation to Crohn's disease and ulcerative colitis. The type of guidance provided by the EMEA will assist biosimilar manufacturers to obtain approval and extrapolate indications, but it is up to manufacturers to make sure they have a suitably strong data set to take internationally when seeking approval.

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