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Extended Abstract

Assessment of Structural and Functional Comparability of Biosimilar Products: Trastuzumab as a Case Study

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Abstract:

Biotherapeutics are protein products generated using recombinant DNA technology and manufactured in prokaryotic or eukaryotic cells. It is often said that "the process is the product" and thereby the effect of the manufacturing process is etched on the final product in the form of its heterogeneity. For any biotherapeutic, the suitable range of the critical quality attributes is defined supported the expected impact of a selected variation on the merchandise stability, safety, and efficacy. For a biosimilar to receive regulatory approval, the manufacturer must demonstrate analytical and clinical comparability with the originator product. As this is mandatory, every biosimilar manufacturer performs this exercise for each biosimilar product under development. However, few reports of thorough evaluation of the quality of biosimilar products are available in the literature. We examined the structural and functional comparability of biosimilars of trastuzumab, a humanized antibody biotherapeutic. The originator product, Herclon (Roche), was compared with four marketed biosimilars: Trasturel from Reliance Life Sciences, Canmab from Biocon, Vivitra from Zydus Ingenia, Hertraz from Mylan. Structural comparability was established using mass spectrometry and spectroscopic techniques like Fourier transform infrared spectroscopy, differential light scattering, circular dichroism, and fluorescence spectroscopy. Stability was compared by performing accelerated thermal stress studies. Functional comparability was established via surface plasmon resonance and biological assays like antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. With respect to comparability, one biosimilar exhibited significant difference in multiple attributes, such as lower percentage of monomer content and main charge variant species, lower percentage of aglycosylated glycoform G0, and lower estimated potency values. Overall, the results indicated general similarity with respect to structure and function, but we found variations with respect to size heterogeneity, charge heterogeneity, and glycosylation pattern in each of the biosimilars.

Introduction:

Srishti Joshi completed his PhD in molecular biology and biochemistry from Massey University, NZ. She is currently an Institute postdoc fellow in Professor Anurag. S. Rathore's group, at the Centre of Excellence, Biopharmaceutical Technology, Indian Institute of Technology, Delhi, India. Her areas of interest include analytical characterization of biologics, biosimilars and higher order structure characterization. Within Prof. Rathore's group, she also fulfills the responsibility of group lead for the analytical characterization team.

The concept of biosimilar was established in the early 2000s in EU. Currently, the regulatory framework for biosimilar has also been established in the US, Japan, and other countries. As of 2018, biosimilars for infliximab, adalimumab, rituximab, trastuzumab, and bevacizumab are approved. During the development of a biosimilar, product quality should be evaluated and compared with those of the reference product extensively. Among the standard attributes of therapeutic antibodies, FcRn binding and related structures are documented to affect the pharmacokinetic profile of the merchandise . Other quality attributes such as antigen binding, glycan structure, and isoelectric point are considered to have a potential impact on the pharmacokinetic profile of the product. Based on the high similarity of the standard attributes of the biosimilar to those of its reference product, comparative non-clinical and clinical studies are conducted. Comparable pharmacokinetic profile of the biosimilar and therefore the reference product is vital for biosimilar evaluation.

This study aims to map patents and patent applications for innovator as well as biosimilar monoclonal antibodies in Europe, and investigates legal challenges associated with patenting the innovator product and alleged infringing activities, focusing on consequences for biosimilar developers. Via an exploratory literature review in PubMed and a database analysis in Darts-ip, Derwent Innovation, and Espacenet, an summary of basic patents and exclusivity rights for a few of the best-selling biologicals is given, supplemented with an in depth analysis of patents taken during the medicine's life cycle via three specific case studies (trastuzumab, bevacizumab, cetuximab). Case law was wont to determine which patents were viewed by biosimilar developers as blocking market entry. For the chosen monoclonal antibodies, the key protection instruments seemed to be the essential patent and therefore the additional protection provided by a supplementary protection certificate. We observed that additional patents filed after the basic patent are hard to obtain and often insufficient in blocking market entry of biosimilars, but can in some cases be a substantial hurdle for biosimilar developers to beat in patent litigation cases or to create around, creating uncertainty on the launch date of a biosimilar on the market. These hurdles, however, seem to be surmountable, given that many cases were won by biosimilar developers. Also, biosimilars can be protected by filing new patents and these mainly pertain to new formulations.

Discussion and Conclusion:

The scientific principles for a biosimilar comparability assessment to the reference product are based on those applied for evaluation of the impact of a change in the manufacturing process of a biotechnological product (as outlined in ICH Q5E guideline . A biosimilar should

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be highly similar to the reference product with regard to quality attributes including structure, physicochemical and biological properties. Any observed differences in quality attributes should be justified by showing that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and efficacy.

The biosimilar therapeutic monoclonal antibodies (mAbs) approved in the EU, the US, and Japan are listed in. The first approved biosimilar mAb was the infliximab biosimilar, an anti-TNFα mAb that is used for treatment of rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and other related diseases. The infliximab biosimilar was approved in 2013 in EU. By September 2018, biosimilar mAbs for adalimumab (anti-TNFα mAb), rituximab (anti-CD20 mAb), bevacizumab (anti-VEGF mAb), and trastuzumab (anti-HER2 mAb) were also approved. In addition, biosimilar for etanercept, a TNF receptor-Fc fusion protein was approved. Currently, biosimilars for other mAbs such as ranibizumab and omalizumab are being developed .