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A case study: Scientific challenges for bioanalytical method development of biosimilars

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According to recent FDA guidance, a Biosimilar is a biological product which is shown to be highly similar to the reference product not withstanding minor differences in clinically inactive components. It is essential to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency. Accurate and reliable bioanalytical and immunogenicity data are critical to demonstrating safety and efficacy of biosimilar and to show comparability between innovator and Biosimilar. Demonstration of comparability between biosimilar and innovator compound could be challenging due to different methods used to establish the strength of the drugs. This may lead to significantly different concentrations between biosimilar and innovator drug. Cell-based potency assays may not be able to detect differences between biosimilar and innovator due to wide acceptance ranges (70% to 130%) used in these assays. If the concentration differences cannot be resolved, it may require two assays to measure pharmacokinetic samples for innovator and biosimilar drugs. Use of two separate assays may indicate that the two products are significantly different and necessitate analysis of both compounds using both assays. Proving similarity of the immunogenicity of the biosimilar and innovator can also be quite challenging due to the fact that these types of assays are generally qualitative. The rate of immunogenicity can be particularly difficult when the incidence of positive response is low. In addition, a small process changes during the manufacturing of therapeutic proteins may lead to significant changes in the rate of immunogenicity. Due to these reasons, it is necessary to develop two robust immunogenicity assays, one for biosimilar and one for innovator, with comparable sensitivity, precision, specificity and drug tolerance. Our labs recently developed bioanalytical assays to support biosimilars of Forsteo® (also known as Forteo®). This presentation will explore above challenges and present solutions using Forsteo® assays as a case study.

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Biosimilars development: Overview

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Biosimilars are increasingly being developed by many companies and used as therapeutics for various diseases worldwide. There is a lot of scope to improve in biosimilar story. Biosimilar products are approved through stringent regulatory pathways in highly regulated markets such as the US, EU, Japan, Canada and Australia following loss of exclusivity of their originator reference product. The development of biosimilar product possesses various challenges such as comparable quality, safety and efficacy to a reference product in addition to other challenges in product development from laboratory to manufacturing scale. Biosimilar from process development, pre-clinical trials and clinical trials up to fill finish meets number of challenges. Quality attributes of monoclonal antibody or bio therapeutic proteins are highly affected by both process and product related impurities. There should be an efficient upstream as well as downstream process to overcome all the bottlenecks and establishing appropriate standards for biosimilarity remains an important area for scientific, legislative and regulatory debate. Cost-effective manufacturing process is a key factor to deliver a biosimilar product into the clinic and the clinical performance of biotherapeutics are highly influenced by manufacturing process. The key factors helps in reducing the cost includes the overall manufacturing process time, high titer producing cells, less number of purification steps, higher recovery and yield of clinically active product. Manufacturing process should be consistent & highly robust. The process includes modern QC & QA procedures, in-process control & process validation. Most importantly, manufacturing process should meet the same standard of originator products and the originator product should be extensively studied during the biosimilar product development. Single use technology applications should be evaluated thoroughly before initiating the uses in a manufacturing facility. The manufacturing processes should be clearly defined, controlled and validated to ensure compliance, clear records and any deviations found that should be investigated and well documented. Manufacturer comprehensively designs the production process taking all relevant guidelines into account.

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