How Can Modelling and Simulation Fuel the Clinical Development of Biosimilars?

The relatively low cost to enter the “generic” market and the size of the biologic drug market make entry attractive. However, the failure rate for biosimilars is deemed high, due to the complex manufacturing process and the high variability expected for biologics. Considering that the associated cost for developing a biosimilar is estimated at US$100 million, there is a high risk-cost relationship in the establishment of clinical biosimilarity. It is therefore of great interest to investigate the possibility to optimise the design of clinical trials of biosimilars in order to increase the studies’ efficiency (e.g., robust results, shorter duration, fewer patients, reduced cost). Because these studies have a great regulatory impact, they must be executed in accordance with regulatory guidelines for the evaluation of biosimilarity.

Modelling and simulation (M&S) has been used in the pharmaceutical industry for more than two decades, and can be of competitive advantage for drug sponsors seeking to improve their drug development process and decision-making. The use of M&S for evaluating pharmacokinetic/pharmacodynamic (PK/PD) relationships can support a biosimilar programme, and offers high regulatory impact. In principle, regulators have accepted that PK/PD, dose-response and longitudinal analyses are more sensitive methods than clinical outcome analysis at a single fixed time-point to detect differences between the originator and biosimilar. Although traditional statistical methods are commonly used for the primary evaluation of pivotal clinical trial data, model-based simulations are increasingly used to optimise the design of clinical PK, PK/PD and outcome studies for biosimilars, by leveraging quantitative knowledge of the new product against the originator. Additionally, the FDA acknowledges that M&S can be useful when designing studies, for example, when determining dose selection and defining the acceptable limits for PD similarity.

Through the efficient use of available public domain data and information on the new product, study design decisions can be made to increase the probability of a successful outcome. By integrating information across dose levels, using longitudinal PK/PD and disease-progression models, uncertainty can be reduced in the estimated PK, PD, efficacy and safety endpoints. The models allow variability within, and between, subjects to be estimated, and it is also possible to simultaneously account for multiple factors to explain variation in exposure and response across individuals, including the formation of anti-therapeutic antibodies.

Using the models for subsequent clinical trial simulation, various study designs can rapidly be explored in silico (doses, sample size, study duration, reduced sampling schedules, inclusion/exclusion criteria, and choice of statistical evaluation method). By simulating multiple virtual clinical studies and calculating the outcome for each study in accordance with regulatory guidelines, the probability of concluding PK/clinical similarity can be explored under various scenarios. The influence of an expected difference between the originator and new product (e.g. 0, 1, 3, 5 or 10%) on
the required sample size can easily be calculated, and the most cost-effective design with a sufficient probability of a successful outcome can then be chosen. These methods are also applicable for bridging results across study populations and therapeutic indications.

**Case Study: Adalimumab Biosimilar PK Study**

When developing biosimilars, clinical trials demonstrating PK and PD similarity of the new product against the approved drug are required, and an insufficient sample size can jeopardise the study outcome. For adalimumab, an anti-TNF-alpha antibody used to treat a variety of autoimmune diseases, PK similarity trials often involve a higher-than-normal number of subjects, as high variability in the PK between patients is anticipated.

To explore whether the sample size of such studies can be reduced, a model-based approach was employed. The optimal number of subjects required for demonstrating PK similarity between a proposed biosimilar and the originator was studied using available literature information on the adalimumab originator, against in-house data on the new biosimilar candidate.

A population PK model for adalimumab in rheumatoid arthritis patients following a 40 mg subcutaneous injection of the EU and US approved formulations was implemented in the clinical trial simulation software Simulo. The effect of patient body weight was also incorporated into the model, along with the influence of anti-adalimumab antibodies. Various study designs, with varying sample sizes, were simulated 1000 times. For each simulated clinical trial, the differences in the maximal drug concentration (Cmax) and the area under the drug concentration-time curve (AUC) between the new product and the reference were evaluated using traditional statistical bioequivalence testing methods. The overall likelihood of having a successful study outcome was eventually predicted for the various simulated study design scenarios.

The analysis indicated that studies including more than 150 subjects did not give any significant improvement in the probability of showing bioequivalence when compared with studies in smaller cohorts. It also showed that a difference in anti-adalimumab antibodies of 15% is likely to decrease the likelihood of successful results being achieved for all pairwise comparisons.

By using this model-based simulation approach, accounting for already available adalimumab data, the number of subjects required to demonstrate PK similarity could be reduced by 40–60%, compared to the originally proposed design. This demonstrated the advantages of using such methods to assist in the design of pivotal PK studies to cut cost and save time. The methodology can also easily be applied for PD markers and clinical outcome endpoints.

**REFERENCES**

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