Biosimilar development: Optimizing PK/PD studies

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Introduction

The need to conduct comparative efficacy trials (CET) in the development of biosimilars is currently under intense debate, with the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) advising that CETs may not be necessary if supported by a sound scientific rationale.[1,2] The United States (US) Food and Drug Administration (FDA) is also indicating that a CET may not always be needed in the development of biosimilar monoclonal antibodies. However, the European Union (EU) Committee on Healthcare Medicinal Products (CHMP) currently still requires such trials, but one might expect that this position may change in the future to align with the international trend.[3]

The waiver of CETs will undoubtedly result in greater emphasis on the quality and pharmacokinetic (PK) data. Here we draw on our two decades of practical experience with biosimilar PK/pharmacodynamic (PD) equivalence studies to address:

A. Justifying the waiver of CETs in the development of biosimilars

B. Considerations for the design of PK/PD biosimilar studies

C. Navigating the potential confounding factors in the conduct of PK/PD biosimilar studies

A. Justifying waiver of CET

To support the waiver of a CET, the applicant will need to submit sufficient justification that the analytical methods used to compare structures, variants and impurities of the putative biosimilar with the reference product can detect all potentially clinically meaningful differences.[4] At least some differences are likely, and the applicant will need to justify that these differences do not impact efficacy or safety; possible justification could include:

- Variant occurs naturally in humans[5]
- In vivo metabolism rapidly eliminates differences[6]
- Variant levels are well below what might have a clinically discernible effect
- Differences in biological activity detected are not relevant based on known mechanism of action
- Difference does not impact potency based on sensitive biological assays

Such justifications require expertise and experience and may involve extensive literature searches and, even, potentially the conduct of additional in vitro testing.

B. Biosimilar PK/PD study design

Biosimilar PK/PD studies are more important than ever

As requirements for CETs are waived, comparative PK/PD studies represent a key component of any biosimilarity program for systemically administered therapies.

The design of the biosimilar PK/PD study depends on various factors, including the PK characteristics of the antibody (target-mediated disposition, linear or non-linear PK, time-dependencies, half-life, etc.) and should consider the recommendations outlined in regulatory guidelines including:

- EMA/CHMP: "Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins"[7]
- EMA/CHMP: "Guideline on the investigation of bioequivalence"[8]
- ICH: "M10 Bioanalytical Method Validation and Study Sample Analysis"[9]
- FDA: "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Guidance for Industry"[10]
- FDA: "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product"[11]

Healthy volunteer studies

Where possible, PK studies are best performed in healthy volunteers, representing a more homogeneous population. Dosing schedules can be tailored to the needs of the study, allowing for complete characterization of the PK profile including the late elimination phase without compromising patient care. Additionally, in healthy participants, variability may be reduced e.g. through elimination of target-mediated clearance related to variable expression of the target in the diseased population and impact of concomitant therapies.[10]

Crossover designs are preferred as they reduce inter-individual variability but are not suitable for drugs with high immunogenicity or an extended half-life such as monoclonal antibodies. Crossover studies also limit the ability to study immunogenicity and require a long washout period, extending the study duration. Thus, frequently a parallel group design represents the best option.

For products administered by more than one route e.g. intravenously and subcutaneously, EMA guidelines recommend investigation of both routes but indicate "it may be possible to waive evaluation of intravenous administration if comparability in both absorption and elimination has been demonstrated for the subcutaneous route using additional PK parameters"; this is also the position of the FDA. In addition, if no data are provided for the intravenous route, partial areas under the curve (AUCs) should be assessed to ensure comparability of both absorption and elimination.[10, 12]

Patient studies

When administration to healthy participants is associated with undue risks, PK studies need to be conducted in patients, e.g. for immunomodulators such as rituximab, and for checkpoint inhibitors.

In the case of oncology studies, to minimize sources of variability it may be optimal to study comparative PK in one of the following settings:

1) In the monotherapy setting, or first-line setting, where patients are in a better clinical condition, or

2) In an adjuvant setting in patients with early cancer, where the tumour burden is low.

Another point to consider is that the PK characteristics of anticancer monoclonal antibodies (mAbs) may change over time, for example due to tumour regression.

Where shedding of the target receptor may occur, EMA guidance recommends measuring shed receptor levels at baseline and, if relevant, during the conduct of the study, to verify the baseline comparability of the treatment groups. Stratification by tumour burden or receptor shedding, if possible, may help to ensure baseline comparability.[10]

Cohort size

Cohort sizes should be increased as much as feasible within the constraints of the study, as larger cohorts can help to mitigate the impact of individual variability. The need for larger cohorts, however, should be balanced against the capacity of the study sites and staffing requirements to ensure maintenance of the high level of attention required for timely completion of study activities.

Maximizing value of PD data

PD parameters contribute to the comparability exercise for some biosimilar programs, although in general for mAbs PD endpoints that correlate with clinical effect are not available. Nevertheless, PD endpoints provide valuable comparative information on the in vivo biological activity of the putative biosimilar versus the reference product. Guidelines suggest using multiple PD markers, if available, to support biosimilarity.[12] When planning to use PD markers as pivotal evidence for establishing similarity, it's advisable to consult with regulators beforehand. Dependent on their nature, PD markers may be less sensitive than PK parameters to detect differences between a biosimilar and a reference product, however, these may become more crucial in the future as they are an expression of the direct or indirect engagement of the drugs with the target. Liquid markers that can be easily accessed in blood or other accessible fluids are of particular interest.

Immunogenicity

Immunogenicity should initially be addressed at the CMC level considering factors such as whether structural variants occur in vivo, presence of aggregates and sub-visible particles, and other impurities such as leachate and host cell derived proteins.[13, 14, 15]

Immunogenicity is often of no clinical significance but in some cases, particularly when present at high titer, anti-drug antibodies may impact PK, reduce efficacy, and can also be associated with adverse events such as injection site and infusion reactions.[16, 17] In the past, immunogenicity has required investigation in repeated dose studies however assays are now far more sensitive and capable of detecting anti-drug antibodies at levels below 10 ng/ml, well below the 100 ng/ml considered to be the threshold for clinical significance.[18,19] This permits comparison of immunogenicity in a relatively small sample size, often even following a single administration to healthy participants.

C. Potential confounding factors in the conduct of PK/PD equivalence studies

There are a number of potential confounding factors in the PK/PD equivalence studies conduct that need to be taken into account. We discuss those listed below in more detail.

- Trial population variability
- Protein content differences in test and reference product batches
- Inconsistent administration techniques
- Sampling and sample processing
- Inconsistency in study condition, team stability and accurate data capture
- Bioanalytical method validation

Trial population variability

Many factors need to be controlled and balanced across arms during selection of the trial participants such as the examples listed below:

- Male/female ratio
- Age
- Weight (weight-dependent exposure can impact results)
- BMI (subcutaneous fat may impact absorption)
- Pre-existing conditions
- Race/ethnicity

The sponsor should aim to match the range of experience from any relevant historic studies used to inform the coefficient of variation (CV%) or when in doubt should choose a more conservative approach. Where CV% is not known or associated with high uncertainty, this can be checked by a blinded interim analysis.

Protein content differences between test and reference product batches

Differences in protein content can profoundly impact the potential to demonstrate PK equivalence. At the extremes of the approved specification, a 10% to 20% concentration difference could occur, whereas statisticians generally allow for accommodation of no more than 3% to 5% of such variability. Current CHMP guidelines state: "Correction for protein content may be acceptable on a case-by-case basis if pre-specified and adequately justified, with the results from the assay of the test and reference products being included in the protocol."[13] The amount of protein administered can also be impacted by differences in the fill volume e.g. of a prefilled syringe or accuracy of the delivery device.

Administration techniques

Special focus should be given to the product preparation and administration. PK parameters can be impacted by factors such as infusion flow rates and angle and depth of injection and incomplete dose delivery. To achieve consistent investigational medicinal product (IMP) preparation and administration, consider limiting the number of staff members responsible for these tasks. A small group of qualified team members should be selected and provided with specialized, in-depth training on the specific techniques required for the biosimilar and its reference product. This focused approach ensures that each administration is performed with the same level of expertise and attention to detail, minimizing variability between participants.

Sampling and sample processing

It is important to ensure that blood samples are taken within the appropriate time window, accurately labelled and correctly stored. Precise timing of PK and PD samples is critical for accurate comparison between the biosimilar and reference product. In addition, maintaining a complete chain of custody for all samples, from collection through analysis, and ensuring consistent sample handling are vital to preserving data integrity in biosimilar trials. Comprehensive staff training on the importance of timely performance of study activities — especially blood sampling and sample handling, emphasizing the critical nature of sampling windows in biosimilar studies should be performed. Developing clear and concise laboratory manuals that detail every step of sample management, from collection to storage and shipping, is advised. In addition, thorough staff training on these procedures, emphasizing the importance of consistency in sample handling should be rolled out.

Leveraging a robust sample tracking system is recommended, possibly utilizing barcode technology, to maintain a verifiable chain of custody throughout the sample lifecycle. In addition, automation of processing steps is recommended where possible to reduce human error and increase consistency, e.g., pre-programming of centrifuges.

Inconsistency in study condition, team stability and accurate data capture

Similar conditions for study conduct across all participants should be ensured. This includes standardizing mealtimes, activity levels, and environmental conditions within the clinical unit.

The study team should be kept as stable as possible throughout the course of the study. This will reduce variability in procedure performance, data collection and processing.

A robust system for seamless capture of study data, ideally utilizing electronic data capture systems with built-in alerts for upcoming activities is recommended.

Bioanalytical method validation

The need for a validated method in the primary matrix (plasma or serum) is essential. Validated PK methods are usually based on quantification of both originator and biosimilar using a single analytical reference standard. As such, an essential element of bioanalytical method development is the demonstration that a calibration line prepared with originator can quantify incurred samples from subjects dosed with biosimilar (and vice versa). Historically, a simple comparison of calibration lines was considered sufficient, however more recently a more comprehensive approach using accuracy and precision (with calibration and quality control crossover) is expected.

Previously, the FDA and EMA had published guidance documents on what should be performed (and how this data should be reported) for both bioanalytical method validation and subsequent sample analysis.[20] Since November 2022 (FDA) and January 2023 (EMA) both Regulatory Authorities have formally adopted ICH M10 as their guidance document for bioanalytical method validation and study sample analysis, and as such have removed any concern over minor differences that existed between their own documents.[9] Method development, validation and samples analysis (as per ICH M10) allow for robust PK data to be generated as part of a biosimilar program. Reporting both validation and study data as per ICH M10 harmonises the type and form of data supplied to Regulatory Authorities, which in turn should minimize queries raised post submission.[9]

Conclusion

For CETs to be waived, any quality differences between the test and reference products will need to be robustly justified as having no potential undesirable clinical impact. This requires a deep understanding of functional activity relationships. In addition, the PK/PD study will need to be thoughtfully designed and proficiently conducted to minimize variability and ensure data integrity in biosimilar trials.

Successful operationalization of biosimilar trials requires meticulous attention to detail in IMP administration, adherence to study schedules, sample handling, and overall study conduct. By applying strategies to address these potential confounding factors, clinical research organizations can significantly enhance the quality and reliability of data generated in biosimilar trials, thereby ensuring their inspection-readiness and facilitating the approval of new biosimilars. Potential sponsors of biosimilar trials should select study sites that have biosimilar expertise and a proven track record in conducting those studies in alignment with the above-mentioned criteria for success.

With two decades of experience in bringing biosimilars to market, Parexel can optimize and accelerate your development programs.

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