# Determining the Preclinical Toxicokinetic Comparability for a Biosimilar Drug

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## Introduction

Programs for biosimilar drugs usually need at least one preclinical study to support the clinical phase of development. This study must have pharmacokinetic, immunogenicity and toxicological components and provide insight into the similarities and differences (i.e., *comparability*) between the biosimilar and the innovator drug. This white paper focuses on one component of such a study: demonstrating the comparability of the toxicokinetics of the biosimilar versus the innovator drug.

## What is toxicokinetic comparability?

The term "comparability" comes from the biosimilar guidelines which can be found on the European Medicines Agency (EMA) web site[1]. These state that at least one non-clinical repeat dose toxicology study with toxicokinetic, immunogenicity and pharmacodynamic endpoints should be considered for a biosimilar. However, the distinguishing feature of the pivotal toxicology study for a biosimilar drug is that the sponsor must demonstrate that the biosimilar and the innovator drug are "comparable" with respect to both toxicity and toxicokinetics.

The former means that the biosimilar and the innovator drug exhibit comparable toxicology profiles. The latter means that it is necessary to determine if the biosimilar and the innovator drug have comparable or similar exposure in an animal model.

The general guidance[2] on developing a biosimilar drug does not specify the mechanics of establishing biosimilarity. Does this mean simply a graph of mean concentration versus time for the biosimilar and innovator for each treatment group, leaving it up to an agency reviewer to make a subjective decision as to whether the drugs are "similar" or "comparable"? Or is the expectation to conduct a full-fledged bioequivalency study in an animal model? The specific guidances[3,4,5,6,7] for erythropoietin, interferon alpha, granulocyte-colony stimulating factor, growth hormone, and insulin do not provide insight into how rigorous an evaluation of toxicokinetics is expected.

## How is toxicokinetic comparability determined?

Where feasible, we have taken the conservative approach and designed preclinical toxicokinetic studies that compare the relative systemic exposure of the biosimilar and the innovator using pharmacokinetic and statistical approaches typically reserved for human equivalence studies.

Designing these studies in animal models requires an adaptation of the approach used for humans. Specifically, for some species, the number of blood samples needed to robustly evaluate the pharmacokinetic characteristics of a drug is a rate-limiting factor in the evaluation. In some EU member states, the extravasation volume and the frequency of exsanguination is limited. For biosimliar compounds, particularly those with long half-lives, this limits the ability to fully characterize and compare the elimination phase. These are complex molecules and slight differences in the biochemical structure may result in differences in systemic clearances between the biosimilar and the innovator compound. In general, the more robust the evaluation, the greater the confidence is in the comparability of the two products.

In most cases we recommend conducting pilot studies in the animal model. From this data we get our first look at the pharmacokinetics of the biosimilar using the clinical route of administration compared to the innovator drug. Lessons learned from these pilot studies help us plan the pivotal study. For example, from the variability in the pilot studies we estimate the number of animals needed, the number of blood samples and the optimal placement of these samples (i.e. time points) for the pivotal animal study.

In toxicology studies, when using a species having a small blood volume, the blood sampling times are staggered. Exposure at any one sampling point is based on a different subset of animals relative to the adjacent sampling points and animals are sacrificed at the time of exsanguination. This limits the exposure evaluation to an average exposure based on the mean

exposure at each of the individual sampling points and consequently limits any inferential statistical comparison.

An efficient toxicokinetic comparability study utilizes a subgroup (e.g., satellite group) of animals for toxicokinetic comparability. Time-matched samples are drawn from each animal in each treatment cohort. This approach provides data which can then be used in a statistical evaluation similar to those applied in human bioequivalence studies. With extravascular administration (e.g. subcutaneous), a pre-dose sample should be included whenever possible particularly for toxicokinetic evaluation following multiple-dose administration.

The toxicokinetic/pharmacokinetic treatment of the data consists of non-compartmental pharmacokinetic analysis (NCA). As described above, wherever possible, the preference is to derive the pharmacokinetic variables using individual animal data as opposed to the mean concentration at each sampling. Non-compartmental analysis of the mean concentration-time profile can be conducted for each treatment where the above mentioned approach is not feasible.

Correction for body weight is made for the relevant NCA parameters. Descriptive statistics for the various treatments are also performed. An analysis of variance (ANOVA) is performed similar to that applied in human equivalence studies, adapted to account for the specific design elements described above. Similar to human equivalence studies, wherever feasible, confidence intervals around the ratio of least-squares means can be constructed to provide insight into the degree of similarity between the biosimilar and innovator product.

## Conclusions

The toxicokinetic comparability exercise is conducted prior to the Phase I human study of the biosimilar. If one can show toxicokinetic comparability in an animal model this does not ensure that the biosimilar will be shown to be bioequivalent in humans. Yet, if designed appropriately, an animal model can provide greater confidence about the drug's potential equivalence and assist in the design of the pharmacokinetic component of the Phase I human study.

## References


1 http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

2 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (2006)

3 Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (revision), 2010

4 Non-clinical and clinical development of similar medicinal products containing recombinant interferon alfa, 2009

5 Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor, 2006

6 Guidance on similar medicinal products containing somatropin, 2006

7 Guidance on similar medicinal products containing recombinant human soluble insulin, 2006