Revised EMA Biosimilars Guidelines: The Impact on Development Requirements, a Nonclinical Perspective
INTRODUCTION

The European Medicines Agency (EMA) recently introduced a number of draft revisions to the biosimilar guidance that was originally introduced in 2005. The revisions to the guidelines are based upon the experience gained through EMAs review of biosimilar applications and address some of the issues raised by the development of more complex biosimilar products. The suggested changes are likely to have a profound and positive impact on how the biopharmaceutical industry develops biosimilars, with a significant proportion of the changes affecting nonclinical program design, in many cases quite radically. This whitepaper will review the recent revisions to the guidance and assess their likely impact on the nonclinical development requirements of biosimilars.

DRAFT REVISION OF THE SIMILAR BIOLOGICAL MEDICINAL PRODUCTS GUIDELINE

A revised draft of the overarching European guideline on the development of biosimilar medicinal products was released for consultation in May 2013. Specifically, the revised guideline:

- standardizes the terminology so that the term “biosimilar” is used in an appropriate manner
- introduces the principle of not following the generic legal basis for biological products (although the details are unclear)
- elucidates the principles of biosimilarity
- refines some of the key aspects of biosimilar product development (e.g., efficacy and safety aspects, discussion on pharmaceutical formulation, posology and route of administration and the acceptable variability for a biosimilar)
- simplifies the text by amending the definition of a biological product rather than providing examples of biological products.

Non-EEA Comparators

In addition to the above, there is one change to the guideline which is of critical importance to nonclinical and clinical development, as well as to the quality documentation for a biosimilars product. The current guideline states that the chosen reference medicinal product must be a medicinal product authorized in the European Economic Area (EEA), whereas the draft revised guideline states that “it may be possible for an applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorized comparator.” In such cases, the reference medicinal product must be authorized by a regulatory authority with similar scientific and regulatory standards as the EMA (i.e., an ICH country).

The lack of opportunity within the European regulatory framework to use data generated with a comparator sourced outside of the European Union has been a major source of frustration and has led to significant additional cost and development time for some products. The use of a non-EEA authorized comparator will not always be possible, but where it has been shown to be similar to the EEA authorized product, the flexibility allowed by the draft revision will be much welcomed. In such circumstances, bridging data will likely be required and will typically include analytical data (both structural and functional data) that compares all three products (the proposed biosimilar, the EEA-authorized reference product and the non EEA-authorized product). Additionally, clinical PK and/or PD bridging data for all three products may be required by the agency. This significant change would put the EMA guidance in line with the recent FDA draft guidance document “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” which was introduced in February 2012 and reflects an increasing collaboration between FDA and EMA. The FDA guidance allows for use of “…data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed product…” where “…adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilar-
ity and to establish an acceptable bridge to the U.S.-licensed reference product.”

In addition to regulatory requirements one also needs to consider the ethical dimension to nonclinical study design, particularly when conducting studies in non-human primates. In our experience European regulators and animal ethics committees are likely to look unfavorably on a non-human primate study which includes two comparator products based on their drive to reduce the number of animals used in drug development, unless there is a very robust scientific justification for conducting the study.

**DRAFT GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES**

In addition to the revised draft overarching European guideline on the development of biosimilar medicinal products, the EMA’s Biosimilar Medicinal Products Working Party (BMWP) has also drafted a revision to the existing guideline for non-clinical and clinical issues related to biosimilar development. The revision, released by the CHMP in June 2013 includes:

+ a risk-based approach for the design of non-clinical studies
+ the use of pharmacodynamic markers
+ study design, choice of appropriate patient population and choice of surrogate endpoints in efficacy trials
+ design of immunogenicity studies
+ extrapolation of indication.

**In Vivo Toxicology**

The current guideline has been revised in light of the development of increasingly complex biosimilar products, and especially biosimilar monoclonal antibodies (mAbs). As alluded to above, in Europe there is significant political pressure to reduce the number of non-human primates used in scientific research. These pressures mean that the number of non-human primates that could be used in a repeat dose toxicology study to compare a putative biosimilar to a reference product would likely be small, and due to the variability in response the relevance of such a study is therefore likely to be questionable.

Furthermore, where such small numbers of animals are used in a study there is an increased likelihood of a false positive result, i.e. observing a difference between the biosimilar and the reference product due to inter-animal variability, when no difference is actually present. Allowing a risk-based approach to the design of non-clinical studies enables the sponsor to make a case for either using a reduced study design, or not conducting a toxicology study in non-human primates at all. Either approach would require a favorable risk assessment which encompasses:

+ the specific outcome of the quality comparability exercise for the claimed biosimilar product
+ specific pharmacological/toxicological properties of the reference medicinal product
+ whether sufficiently sensitive *in vitro* functional assays predictive for *in vivo* pharmacodynamics/toxicity of the claimed biosimilar product are available
+ the feasibility and relevance of *in vivo* testing in a relevant species.

Such an approach would require a very well characterized biosimilar product and a rigorous and scientifically valid justification, but there seems to be real will amongst regulators in Europe to allow a flexible approach to the non-clinical strategy for biosimilars. Whilst not stating MHRA or EU policy David Jones and colleagues from the MHRA indicated in an article...
in June 2012 that for complex biosimilars such as mAbs, “While no compromises in patient safety and integrity are acceptable, we believe that in vivo studies using a limited number of animals are generally not capable of detecting minor differences in biological effects caused by subtle differences between reference and putative biosimilar products even if fairly high doses are used. Furthermore, if a difference was identified in an in vivo nonclinical study, the clinical relevance of this could only be determined by studies in human subjects.”

The possibility afforded in the draft revised guideline to extrapolate from one indication to another will also need to be considered when designing a nonclinical safety program for a putative biosimilar product. Additional in vivo nonclinical studies are not likely to be required to support such an extrapolation, but it is likely that additional in vitro studies will be required in different target cells where there are differences in the intracellular signaling pathways. Where different active sites of the product or different receptor are involved in the mechanism of action for other indications additional in vitro studies are very likely to be required and the need for further in vivo studies should also be considered.

DRAFT GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES

A draft revision to the guideline on quality issues associated with the development of biosimilars was released for consultation in 2012. Whilst this document does not address non-clinical issues per se, the outcome of the quality comparability exercise described in the guideline has a significant bearing on non-clinical study requirements, and indeed on whether a product can be described as a biosimilar at all. Whilst the revised guideline does add significantly to the detail of what is required as part of the quality comparability exercise, many still seek further detail. The EMA has responded with a call for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development in a draft concept paper. The document recognizes sponsors’ difficulty in understanding the quantitative and statistical requirements of the quality comparability exercise for biosimilars in particular, but also for other biologicals and small molecules.

DRAFT GUIDELINE OF THE NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT HEPARINS

A revised draft European guideline on the development of biosimilar low molecular weight heparin (LMWH) products was issued in January 2013 (consultation ended in July 2013). A guideline on the nonclinical and clinical development of biosimilar LMWHs already exists but there are critical changes in the nonclinical requirements of this revision relating to both the in vivo pharmacodynamic and toxicology testing requirements. In the draft revised guideline, more flexibility is allowed in the need to conduct in vivo pharmacodynamic assessment of the biosimilar.

The draft revised guideline states that “If physicochemical and biological characterization of the biosimilar and the reference LMWH has been performed with a high
level of resolution and convincingly demonstrated close similarity, in vivo studies are not required as part of the comparability exercise." The existing guideline, on the other hand, indicates that an in vivo pharmacodynamic assessment should be conducted.

The existing guideline states that “Data from at least one repeated dose toxicity study in a relevant species (e.g., the rat) should be provided." The guideline goes on to indicate that the duration of the study should be at least 4 weeks, that it does not need to include toxicokinetics (TK) (due to technical difficulties in analysis of LMWHs) and that local tolerance testing can be included as part of the repeat dose toxicity study. In comparison, the revised draft guideline states that “generally, separate repeated dose toxicity studies are not required, except where in specific cases (e.g. when novel excipients are used).

These changes to the requirements for the nonclinical testing of biosimilar LMWHs constitute a significant change and are likely to represent a significant reduction in the overall nonclinical study requirements for well characterized biosimilar LMWHs. The heterogenic nature of LMWHs, the well understood link between in vitro and in vivo pharmacodynamic effects, and importantly the fact that dose limiting toxicity is so closely related to the pharmacological action of the product means that in vivo toxicity studies are unlikely to add significantly to the risk assessment of a biosimilar LMWH before conduct of a First Time in Human clinical study. In vitro comparative assessment of anti-FXa and anti-FIIa activity should therefore be sufficient to compare the efficacy and likely safety (as the dose limiting toxicity is related to the pharmacologic action) of a biosimilar LMWH. However, whilst the draft revised guideline also allows for a well characterized biosimilar LMWH to progress into clinical trials without any in vivo data, it seems likely that some clinical investigators would be uncomfortable with the lack of any in vivo pharmacodynamic data. Also, as rodents are suitable models for safety testing of LMWHs, the arguments relating to small group sizes relevant to development of monoclonal antibodies are not relevant for biosimilar LMWHs. Hence, if the guidelines are adopted unchanged, it is likely that some clinical investigator education may be required to address their concerns regarding the lack of in vivo data, and some sponsors may elect to progress into clinical testing only once some in vivo data is available.

IN SUMMARY

Many of the changes in these latest draft European revisions bring the guidelines more in line with other international bodies. In particular the opportunity to use a non-EEA sourced comparator in clinical studies is consistent with the approach taken by the U.S. FDA. This change is likely to be seen as a significant advantage to some sponsors and have a marked impact on the global development strategy. The revisions also allow sponsors more flexibility in the design of nonclinical safety studies, and in certain circumstances allow them to be waived completely. Utilizing the full flexibility that the revisions allow for nonclinical development will, however, need to be considered carefully to ensure that the approach taken satisfies not only general regulatory requirements, but requirements specific to the product class, the specific product as characterized in the quality package and cross-functional development needs. Furthermore, acceptance of a reduced nonclinical program or innovative approach will only be gained when accompanied by a scientifically robust justification.
REFERENCES


3. Christley RM. Power and error: increased risk of false positive results in underpowered studies. The Open Epidemiology Journal (201) 3: 16-19


