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EMA DRAFT GUIDELINES FOR BIOSIMILAR ANTIBODIES RELEASED

On November 18, 2010, the European Medicines Agency (EMA) released draft versions of two guidelines relating to the regulatory approval of monoclonal antibodies: the "Guideline on biological medicinal products containing monoclonal antibodies"[1] and the "Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use".[2] Both guidelines are now subject to public consultation until May 31, 2011.

The former regulation for the approval of biosimilar monoclonal antibodies (mAb) was long-awaited by the pharmaceutical industry, as many basic patents for therapeutic mAb will expire within the next couple of years. The present guideline sets forth the non-clinical and clinical requirements for mAb-containing medicinal products claiming to be similar to another one already marketed (*i.e.*, biosimilars) and complements several previous guidelines for biosimilar medicinal products, based on which 13 such products have been approved so far in Europe.

The second guideline on the immunogenicity assessment of mAb that was released by the EMA is applicable to all biological medicinal products containing mAbs, not just biosimilars.

1. Guideline on mAb-containing biosimilars

In general, the guideline requires a biosimilar antibody not be inferior in quality, efficacy, and safety with regard to the reference antibody, which is a lesser

[1] EMA/CHMP/BMWP/403543/2010
[2] EMA/CHMP/BMWP/86289/2010

standard than for a new non-generic drug. In particular, the Guideline states that "[t]he focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit *per se*, which has already been established by the reference product."[3]

In order to establish such biosimilarity, deviations from the guidelines need to be fully scientifically justified. Both *in vitro* and *in vivo* studies will be required for regulatory approval. The guideline stresses that the scope and amount of testing to be performed will be determined on a case-by-case basis.

The guideline is intended to provide product-specific guidance that presents the current view of the EMA on the demonstration of biosimilarity of two mAb-containing medicinal products. While the new guideline is specifically directed to mAbs, it states that "the principles discussed may also, on a case-by-case basis, be relevant to related substances like, for example, fusion proteins based on IgG Fc." However, "[s]econd- or next-generation biologicals […] that are structurally and/or functionally altered, in comparison to already licensed reference products, to gain an improved or different clinical performance" (*i.e.*, biobetters) are beyond the scope of the gideline

NON-CLINICAL STUDIES

In general, the guideline calls for a risk-based approach to evaluate a mAb on a case-by-case basis. Non-clinical studies should be performed before initiating clinical development. *In vitro* studies are to be conducted first and then a decision is to be made as to what, if any, *in vivo* work will be required.

More specifically, in order to assess any difference in biological activity between biosimilar and reference products, data from a number of comparative in vitro studies should be provided.[4] These should include relevant studies on: binding to the target antigen; binding to all Fcγ receptors, FcRn and complement; Fab-

[3] Cf. Guideline, Executive Summary, page 3, lines 66-68; Introduction, page 4, lines 93-98.
[4] Cf. Guideline, Section 4.1, page 5.

associated functions (e.g., neutralization, receptor activation or receptor blockade); and Fc-associated functions (ADCC and CDC assays, complement activation).

These concentration/activity studies should be comparative in nature and should be designed to exclude all differences of importance in the concentration-activity relationship between the biosimilar and reference products and should not just assess the response *per se*. Taken together, these assays should cover all functional aspects of the mAb even though some may not be considered necessary for the mode of action in the clinic.

Once the above-studies have been completed, the need for additional *in vivo* non-clinical studies must be evaluated.[5] Factors that will be considered include (but are not restricted to): differences in process related impurities due to a different cell expression system compared with the reference product; the presence of a mixture of product-and/or process related impurities that can be less well characterized; significant differences in formulation, use of not widely used excipients; the need to test the biosimilar mAb directly at therapeutic dose in patients, rather than in healthy volunteers; availability of a relevant *in vivo* model.

If the *in vitro* pharmacodynamic (PD) studies are considered satisfactory, and none of the above factors is considered a concern, then an *in vivo* animal study will not be considered necessary.

However, if that is not the case, then the need for comparative studies should be decided on a case-by-case basis. If an *in vivo* study is deemed necessary, animal studies are to be designed to maximize the information obtained (PD, PK (pharmacokinetics) and/or safety). However, the conduct of large comparative toxicological studies in non-human primates is not recommended, nor is the conduct of toxicity studies in non-relevant species.[6]

[5] Cf. Guideline, Section 4.2, pages 5-6.
[6] Cf. Guideline, Section 4.3, page 6.

CLINICAL STUDIES

Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions, and the applicant should justify that the model is relevant and sensitive to demonstrate comparability in relation to efficacy and safety in the indication(s) applied for. In principle, "the most sensitive clinical model should be used in a homogeneous patient population, since this reduces the variability and sample size needed to prove equivalence, and can simplify interpretation."[7]

Applicants should focus on the patient population where pharmacokinetic equivalence to the reference antibody can be studied with sufficient sensitivity. This patient population may be different than those in the efficacy trial. Equivalence margins will need to be defined a priori and appropriately justified.

For cytotoxic mAbs in anticancer indications, the design of the study should take into account that the PK of cytotoxic mAbs may be time dependent, since the tumor burden may change after multiple dosing. Where multiple therapeutic regimens are licensed for the reference mAb, the comparative PK study should be designed to demonstrate clinical comparability selecting the most sensitive key PK parameters. However, there will generally be no need to test all therapeutic dosage regimens.[8]

PK studies can be combined with PD endpoints, where available. With regard to pharmacodynamic evaluation, there is often a lack of specific PD endpoints. Therefore, the emphasis will often be on non-clinical PD evaluations, e.g., *in vitro* testing.[9]

If PD studies do not convincingly demonstrate comparability of biosimilar and reference products in a clinically relevant manner, similar clinical efficacy should be demonstrated in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blinded and normally equivalence trials.[10]

[7] Cf. Guideline, Executive Summary, page 3, lines 68-70.
[8] Cf. Guideline, Section 5.1, pages 6-9.
[9] Cf. Guideline, Section 5.2, page 9.
[10] Cf. Guideline, Section 5.3, pages 9-10.

In cases where PD studies are suitable to provide the pivotal evidence for equivalence in clinical efficacy, applicants will have to provide sufficient reassurance of clinical safety, including immunogenicity. Study of unwanted immunogenicity is especially important where a different expression system is used for the biosimilar mAb compared to the reference mAb. In most cases, similar pharmacovigilance activities as those of the reference mAb will be required. Pre-licensing safety data should be obtained in a number of patients sufficient to determine the adverse effect profiles of the biosimilar mAb. As regards immunogenicity assessment, applicants should refer the existing EMA guidance (cf. below).[11]

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. If evidence for biosimilarity is based on PD and for the claimed indications different mechanisms of action are relevant, then relevant date to cover pharmacodynamics for all claimed clinical indications should be provided.[12]

Finally, applicants are required to present a pharmacovigilance and risk management plan in accordance with current EU legislation. Such plan must include post-authorization studies which will evaluate: (1) the safety of extrapolated clinical indications of the mAb, (2) occurrence of rare and serious adverse effects previously shown by reference product, and (3) detection of novel safety signals. The EMA admits that this concept may have to exceed routine pharmacovigilance.

However, despite the release of the present guideline for biosimilar mAbs, the EMA does not expect to be flooded with applications for biosimilars. It is commonly expected that there will be only 2-3 new applications per year. TL011, a biosimilar version of Rituximab/MabThera (produced by Teva Pharmaceutical), is considered to be one of the first candidates as this mAb has entered early stage clinical trials.

[11] Cf. Guideline, Section 5.4, pages 11-12
[12] Cf. Guideline, Section 6, page 12.

2. Guideline on immunogenicity assessment

This guideline seeks to address the problems associated with detection of and risk related to the development of the mAb immune response. Unfortunately, it does not offer much real guidance but rather mostly runs out in the description of complications involved in controlling immunogenicity. Providing a general framework is an almost impossible task in this subject area given the many differences between mAbs, but the key thread appears to be comprehensive risk planning at the early stages of development and commitment to diligent monitoring post-approval.

The guideline particularly focus on the problems manufacturers may experience with current assays used to assess mAb immunogenicity.[13] The guideline advocates a risk-based approach, however, acknowledging that it is a mere starting point, as standards for immunogenicity assessment of mAbs cannot be easily generalized. Nonetheless, product, process, and patient-related risk factors are usually involved. Each factor within each group must be ranked and justified early in product development, with higher-ranked risk factors requiring more stringent clinical trials. Product factors include the selectionof cell line, potential impurities, product isoforms and degradation products. The route of administration is an example of a process risk that must be considered. Patient risk factors such as age, genetic background, and underlying disease must also be taken into account.[14]

Most importantly, the guideline puts emphasis on the evaluation of clinical consequences of unwanted immune response for each mAb. The mode of mAb action is critical in this assessment, as many mAb lyse or induce apoptosis in cells. Also important is whether adverse events such as infusion reactions can be properly handled by neutralizing the mAb with other antibodies or with medication. One standard requirement is that all mAb will require a validated screening assay followed by a validated neutralizing assay. All antibodies must be classified as neutralizing or non-neutralizing, regardless of their risk level. Patient samples should be undertaken as a routine basis, tested in real-time, and banked during the course of development.

[13] Cf. Guideline, Section 7, pages 6-8.
[14] Cf. Guideline, Section 4, pages 4-5.