



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON SIMILAR
BIOLOGICAL MEDICINAL PRODUCTS CONTAINING MONOCLONAL ANTIBODIES**

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1. INTRODUCTION

Monoclonal Antibodies (mAbs) comprise a large important class of therapeutic biologicals. Different mAb products share some properties, e.g. on a functional level, but differ in aspects like the mechanism of action. The complexity of mAbs is a challenge for the development of new mAb products that are claimed to be similar to marketed mAbs. Nevertheless, such mAbs are being developed, and CHMP has given scientific advice for the development of some individual products. This guideline lays down the non-clinical and clinical requirements for monoclonal antibody-containing medicinal products claiming to be similar to another one already marketed, i.e. similar biological medicinal products (biosimilars). It may also include a chapter on quality aspects more pertinent to biosimilar monoclonal antibodies, should BWP/BMWP consider it necessary. The non-clinical section addresses the pharmacotoxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan.

2. PROBLEM STATEMENT

Guidance for development of biosimilars is already available, including class-specific guidance. With monoclonal antibodies, a next step is taken towards more complex and large molecules. Whilst available guidances (Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, CHMP/49348/05; Production and Quality Control of Monoclonal Antibodies and Related Substances, CHMP/BWP/157653/07) appear to provide sufficient guidance on quality of biosimilar mAbs, there are several issues pertinent to non-clinical and clinical development that are not sufficiently covered by current guidances. There are several areas of increased complexity as regards design of a biosimilar development programme in these fields, which require careful consideration and exploration of further science-based approaches.

The guideline has in its main focus monoclonal antibodies, but principles may also be applicable to related proteins like, for example, fusion proteins.

3. DISCUSSION

Monoclonal antibodies have been established as a major product class of biotechnology-derived medicinal products. On one hand, they are structurally complex, and may have several functional domains within a single molecule, depending on the isotype (antigen-binding region, complement-binding region, constant part interacting with Fc receptors). On the other hand, various assays have been established in the past years that allow for thorough characterisation of complex proteins. Regarding structure, whilst an identity at the amino acid sequence level is, in the current understanding, a prerequisite for a mAb to qualify as a potential biosimilar, further consideration may be required on the degree of similarity required for other quality attributes, such as conformation and post-translational modifications in the Fc region. The guidance may also have to discuss some more practical aspects pertinent for a biosimilar mAbs development. However, BMWP and BWP will have to explore to what level of detail such guidance is helpful or not, and if such advice would be generally applicable.

For non-clinical development, toxicology is usually tested in a relevant animal species, since in non-relevant animal species a given mAb will not be active, thus either resulting in no toxicity, or in artificial toxicity findings that are not readily predictive for dosing in humans. Due to the specificity of mAbs the relevant species is in most cases a non-human primate species or even the chimpanzee. In these circumstances, the conduct of large comparative toxicity studies may not be feasible or ethically acceptable. Instead, experience gained with numerous mAbs over the past decade(s) will have to be considered, together with a differential discussion on the toxicity that should be in the focus (specific toxicity, based on the mechanism of action; or unspecific toxicity, based on impurities etc) and to what extent non-clinical pharmacodynamic studies can be done or are even needed in view of the clinical data to be gathered (see below).

For clinical development, the currently licensed mAbs comprise several main categories for their mechanism of action:

- 1) Immunomodulators, e.g. anti-TNF-alpha mAbs;
- 2) Cytotoxic mAbs with or without receptor modulation, e.g. anti-CD20, anti-EGFR mAbs or anti-Her2 mAbs;
- 3) Others which do not fall under these categories, e.g. antimicrobial mAbs like anti-RSV mAbs.

For a biosimilar development, which is strictly comparative in nature, clinical trial designs need to be explored that will provide sufficient reassurance of equivalent efficacy and comparable safety of a biosimilar mAb to a reference mAb. Thus, the feasibility of the study designs and endpoints used to develop the reference product needs to be re-evaluated for the development of a biosimilar product. The guidance document will have to discuss several key aspects, including how extrapolation of efficacy and safety should be handled, e.g. from one autoimmune condition like rheumatoid arthritis to another like Crohn's disease, or from an autoimmune condition to an anti-cancer indication and vice versa.

For primary endpoints, a discussion is required on the approach to demonstrate biosimilarity, i.e. should the endpoint be the most sensitive endpoint to establish biosimilarity, or should it be a clinically relevant endpoint. Considerations will have to include the severity of the condition (e.g. cancer, or autoimmunity), the heterogeneity of the patient population that can itself hamper the biosimilarity exercise, and the feasibility of clinical trial design, e.g. as regards the number of patients that would be required. It also needs to be discussed if an endpoint for a biosimilar mAbs development may be different from those proposed by available clinical CHMP guidance for novel medicinal products that require a stand alone development programme.

As regards unwanted immunogenicity, another paper specific for mAbs is currently under preparation (Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use, EMEA/CHMP/114720/2009). BMWP will discuss whether issues more specific to biosimilar mAbs should be included in EMEA/CHMP/114720/2009, or if they should be included in the guidance on biosimilar mAbs.

Finally, a discussion on the potentials of a well-planned post-marketing safety follow-up to complement information obtained for approval of a biosimilar mAb is necessary.

4. RECOMMENDATION

The Biosimilar Medicinal Products Working Party (BMWP) recommends drafting a guideline on the applicability of the biosimilar approach for monoclonal antibodies intended for in vivo clinical use.

The main topics to be addressed include:

- Potentially a short discussion of quality attributes and potential practical aspects as they relate to biosimilarity, should it be necessary and feasible.
- Non-clinical development: Need or not for a comparative pharmacodynamic and/or toxicology study in a relevant species, and discussion of potential alternatives. Discussion on whether there should be a focus on target-related toxicity, or unspecific toxicity e.g. of impurities.
- Value of comparative cross-reactivity studies, and also discussion of whether the target is soluble, membrane-bound or both.
- Possibilities for demonstration of biosimilarity (or demonstration of lack of differences) arising from pharmacodynamic measures and in vitro assays, e.g. potency assays, analysis of signalling modulation, etc.
- Relevant endpoints for efficacy, or safety, to establish biosimilarity. Discussion on how clinically relevant information may be enhanced by other endpoints and long-term extension of studies, besides the primary endpoint that concentrates on biosimilarity.
- A discussion on extrapolation of clinical efficacy and safety, including aspects like sometimes insufficient knowledge on the mechanism of action, or potential unknown mechanisms of action that mediate a therapeutic effect.

- Expectations, potentials, and limitations of post-marketing evaluation of safety and potentially efficacy for biosimilar mAbs.

It may be expected that the guideline will comprise two main clinical chapters, since the approach to establish biosimilarity may be different:

- (1) For mAbs with primarily cytotoxic mechanism of action (mainly anti-cancer mAbs);
- (2) For mAbs with immunomodulatory mechanism of action.

Other mAbs not falling under these two main groups may for the moment not yet be explicitly discussed; however, the guideline principles may also be applicable and relevant for them. The BMWP considers that product-specific (i.e., INN-specific) guidance is not appropriate at the current stage. However, BMWP will consider giving more specific recommendations on certain aspects e.g. the disease model to be studied.

5. PROPOSED TIMETABLE

Release for consultation in October 2009, deadline for comments **31 January 2010**.

6. RESOURCE REQUIREMENTS FOR PREPARATION

An expert drafting group within BMWP in consultation with EWP, BWP, BPWP, SWP and PhVWP will develop this guideline. At least 2 formal meetings of the drafting group will be required in the margins of the working party meetings. A closed workshop will most probably have to take place prior to finalisation of the draft guideline, given the anticipated considerable impact of this guidance.

7. IMPACT ASSESSMENT (ANTICIPATED)

Guidance on the investigation and assessment of biosimilar mAbs intended for in vivo clinical use will ensure a more rational and systematic approach for the development and assessment for this large class of biologicals by industry, academia and regulators. Since biosimilar mAbs are already under development, the guidance is expected to give more reassurance as regards regulatory expectations. It may also enhance reassurance in patients and physicians, since the requirements are expected to find a balance between establishing equivalent efficacy and safety on one hand, but feasibility of clinical trials on the other.

8. INTERESTED PARTIES

Competent authorities of the member states, pharmaceutical industry, and academia.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

NA