EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 September 2011
EMA/CHMP/BMWP/572828/2011
Committee for Human Medicinal Products (CHMP)

Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Agreed by BMWP	**September 2011**
Adoption by CHMP for release for consultation	22 September 2011
End of consultation (deadline for comments)	31 December 2011

The proposed guideline will replace guideline on Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, CHMP/BMWP/42832/2005.

Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

Keywords	Similar biological medicinal products, nonclinical studies, clinical studies, recombinant proteins, safety, pharmacovigilance, immunogenicity

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1. Introduction

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005) lays down the non-clinical and clinical requirements for a biological medicinal product claiming to be similar to another one already marketed. This guideline came into effect in June 2006. Since then several biosimilar products have come into the EU market, the number of scientific advices given by the CHMP on the development of biosimilar products has increased significantly and the regulatory framework is becoming wider, e.g. the draft guideline of the biosimilar monoclonal antibodies is being finalised.

2. Problem statement

An increasing number of biosimilar products are under development, especially biosimilar monoclonal antibodies. The development of more complex biosimilar medicinal products is challenging, and several issues in the development are under re-evaluation. These include the selection of relevant species for non-clinical studies, need for clinical equivalence studies and other issues of the design of the pivotal clinical studies, role of biomarkers, amount of immunogenicity data needed, and the possibility to extrapolate to other indications. The WHO Guidelines on Evaluation of Similar Biotherapeutic Products with detailed recommendations on clinical development were published in October 2009. In addition, the EMA is emphasizing the need to follow the 3 R principles (replacement, reduction and refinement) with regard to the use of animal experiments. All these factors suggest revising the current guideline.

3. Discussion (on the problem statement)

There are several issues that require discussion for a potential revision in the guideline.

According to the principles of 3 R the number of animal experiments should be reduced. The finding of a relevant species is challenging especially when considering the development of monoclonal antibodies and potentially other more complex biotechnological medicinal products, as often only non-human primates can be considered to give useful information. The current guideline recommends e.g. to consider at least one repeat dose toxicity study. The number of animals that can be used would probably be small, and the relevance of such a comparative study in non-human primates can therefore be questionable.

With regard to the phase I studies the guideline recommends the selection of relevant pharmacodynamic markers, but such markers are not always available and/or cannot be shown to reflect efficacy.

On the other hand, when relevant surrogate markers do exist, the current guideline includes the possibility of using them (e.g. absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor) as the primary end points in the pivotal phase III studies. This aspect could be expanded to further elaborate on the underlying principles, potentially including examples from other therapeutic areas e.g. oncology.

The current guideline does not mention any recommendations on the patient population in the pivotal phase III studies. In principle, the most sensitive disease model to detect differences should be used in a homogeneous patient population to reduce variability. Many biological products e.g. monoclonal antibodies, have several approved indications, and the principle emerges that the most sensitive one of them should be chosen to show therapeutic similarity. When efficacy and safety has been shown in one indication, extrapolation to the other indications is already now possible under certain circumstances.

The BMWP intends to discuss these criteria and potentially revise or amend them with the experience gained so far.

The current guideline does not tackle the issue of an alternative to the equivalence design, which is currently expected for clinical studies to show sufficient similarity in efficacy (mentioned e.g. in the Draft Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies). In the equivalence trial clinically meaningful differences including superior efficacy between the biosimilar and the reference product are excluded if the 95 % confidence interval of the treatment difference is fully contained within the pre-specified two-sided (upper and lower) comparability margins. In the case of a non-inferiority study, only the lower margin is defined, i.e. the statistical analysis can only show that the product in not inferior to the reference product, but cannot exclude the possibility that the biosimilar product would be better than the reference product. The number of patients needed for an equivalence trial tends to be larger than that for the non-inferiority trial. In the step wise comparability development process (quality, nonclinical, PK, PD) it would be unlikely that superiority would be found in a phase III study. This issue has been extensively discussed in the current WHO biosimilar guideline.

With regard to the immunogenicity data, one-year follow-up data are requested in the current guideline in case of chronic administration. The guideline does not inform requirements for products not intended for chronic administration. With regard to the measurement of antibodies, an optimal sampling schedule should be considered in order to take into account e.g. the onset and duration of the antibody formation as shown by the data of the reference product. Biosimilar products produced with modern technologies may result in a reduced immunogenicity as compared to the reference product, and the BMWP will discuss if these products would still qualify as biosimilar.

4. Recommendation

The BMWP recommends revising the guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues.

Non-clinical issues:

Risk-based approach for design of an appropriate non-clinical study programme

As a basis to decide if and to what extent non-clinical *in vivo* pharmacodynamic and/or toxicological studies should be part of the comparability exercise, a revised version of the guideline will consider a risk-based approach which takes into account e.g.:

- the specific outcome of the quality comparability exercise for the claimed biosimilar product as a biotechnology-derived protein
- specific pharmaco-toxicological properties of the active substance (as reported for the reference medicinal product)
- (non-)availability of sensitive *in vitro* functional assays predictive for *in vivo* pharmacodynamics/toxicity of the claimed biosimilar product
- the feasibility and relevance of comparative/non-comparative *in vivo* testing in a relevant species.

Clinical issues:

The guideline should be clearer with regard to the need of pharmacodynamic markers in addition to the PK parameters in phase I studies. The BMWP will discuss, in case relevant markers are not available and similarity has been shown with selected PK parameters, whether the development of a biosimilar product can proceed to the pivotal phase III studies.

With regard to the design of the phase III studies, the BMWP intends to update the guideline to include examples of surrogate endpoints which are being already recommended in various other biosimilar guidelines, e.g. in the Draft Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies. The BMWP will discuss on how to further define considerations around acceptance of pharmacodynamics markers for demonstration of clinical similarity, and how to generate sufficient safety data in addition.

Also the possibility of using a non-inferiority design in the pivotal phase III studies in certain cases will be considered.

The extrapolation to other indications which are not investigated during the clinical development program of the biosimilar product will be discussed.

The study designs needed to test immunogenicity shall be revisited, also the question whether a biosimilar product can show less immunogenicity than the reference product.

5. Proposed timetable

Release for external consultation: September 2011

Deadline for external comments: December 2011

It is anticipated that the draft revised guideline will be released for consultation in the first semester of 2012.

6. Resource requirements for preparation

The BMWP experts will develop the revision of the guideline. At least one formal meeting of the drafting group will be required in the margins of the working party meetings.

7. Impact assessment (anticipated)

Anticipated benefit for industry (potentially reduced and/or specified requirements) and assessors of biosimilar products.

8. Interested parties

Pharmaceutical industry and competent authorities of the member states, CHMP and its working parties, especially SAWP

9. References to literature, guidelines, etc.

Guideline on similar biological medicinal products (CHMP/437/04)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMEA/CHMP/49348/05)

Draft guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010)

Guideline on evaluation of similar biotherapeutic products (SBPs), WHO 2009

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo use (EMA/CHMP/BMWP/86289/2010 Rev.2)

ICH topic S6 – Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

ICH E10 Choice of control group in clinical trials (CPMP/ICH/364/96)

Guideline on the choice of non-inferiority margin (CPMP/EWP/2158/99)