

Comments to CHMP Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance:

Non-clinical and clinical issues (EMEA/CHMP/42832/2005)

In May 2005 the EMEA Committee for Medicinal Products for Human Use (CHMP) issued for public consultation a draft Guideline on “Similar Biological Medicinal Products containing biotechnology-derived proteins as active substances: Non-Clinical and Clinical Issues”.

EBE, the Emerging Biopharmaceutical Enterprises group, directly represents 69 biopharmaceutical companies – mainly Small & Medium-sized Enterprises – in Europe, which are researching and developing new treatments using biotechnological methods. Therefore, EBE members particularly welcome the EMEA and CHMP’s initiative to consult all interested parties on this draft Guideline and are pleased to be able to contribute to this document providing general and more specific comments in the following pages.

GENERAL COMMENTS

1. Comparability must remain an element linked to changes relating to an identified single product (i.e. one defined manufacturing process and manufacturer, and defined starting material from the same defined source). A definition of comparability and similarity should be included in all guidance documents relating to similar biological medicinal products.

– Comparability will never be possible between a biosimilar medicine and a reference product because comparability should always be based on an assessment of changes strictly related to the same single product within the scope of one defined process for one defined manufacturer.

– The objective of a similarity exercise will always be to evaluate whether the inevitable differences between the biosimilar medicine and the reference product will entail safety and efficacy consequences, which will have a negative impact on the benefit/risk balance of the biosimilar medicine.

2. Non-clinical studies

– Comparative non-clinical studies designed to demonstrate differences (and not a response *per se*) are essential in order to prove similarity with the reference product.

– As long as the impact of differences in physicochemical and biological parameters on clinical safety and efficacy has not been experimentally validated, such results can only give indications concerning potential issues (which have to be addressed during the clinical studies) but are not adequate to replace sufficiently powered clinical studies addressing

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safety (including immunogenicity) and efficacy.

- In view of this, the benefit of non-clinical data, and later clinical data, will be only meaningful when put into perspective of the relevant quality data. Therefore the development of a biosimilar medicine should always start with the generation of appropriate quality data.

3. Clinical Studies (section 4):

- The guidelines should be more specific on the number of comparative PK/PD studies, and whether their objective is to bring complementary data or simply demonstrate reproducibility of the result. Due to the complexity of biological products, the importance of complementary data should be emphasised. The approach in the guidelines would be one of defining a PK programme based on one side on PK studies designed to evaluate the product profile per se, and on the other side to compare the biosimilar medicine with the reference product.
- The same issue is valid for clinical studies. In fact, it seems very difficult to define an evaluation of similarity based on comparative clinical studies only. A company developing a biosimilar medicine should consider for the development programme the benefit of exploratory trials, e.g. human pharmacology and therapeutic trials, and utilise the data obtained in order to properly design therapeutic confirmatory trials.

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It will be very important to consider the role of exploratory trials in order to evaluate the product in the target indication in healthy volunteers (because of the availability of treatments, it would be unethical to test the similar medicine directly in patients without exploratory data), to evaluate and confirm the relevant doses if unknown, and provide an adequate platform for confirmatory trials in terms of design, methodology and endpoints (only validated surrogates, already accepted for the reference product will be acceptable for a biosimilar medicine). Equally, the need for confirmatory trials and comparative trials should be carefully evaluated. In this respect a non-inferiority design with clinically relevant non-inferiority limits will be acceptable.

This will always have to be understood within the scope of a **global approach to similarity**, i.e., an approach taking into account the available information and knowledge relating to the quality aspects of the product, taking into account source materials, formulation issues, the process and all elements relating to quality control, i.e. in-process controls and final testing with the availability of the proper reference standards.

Furthermore, with regard to comparative studies, these studies should also evaluate the immunogenic potential of the biosimilar medicine, because a comparison of immunogenicity of innovative and biosimilar protein products can only be made in comparative clinical trials. Therefore, in the interest of patient safety, no protein drug should be approved without data on its immunogenic properties obtained in clinical studies of adequate size and duration (e.g., in the case of chronic administration, one-year follow-up data will be required).

As the patients' immune system may be influenced by the disease as well as by co-medication the incidence and clinical phenotype may be different for the same product when used in additional indications for which authorisation is sought. During these studies, the formation of anti-product antibodies has to be analysed carefully with sensitive and compound-specific validated analytical assay methods, and their correlation with clinical findings has to be investigated.

- Concerning extrapolation from one indication to another one, the case-by-case approach is acceptable as extrapolation may be possible under certain conditions, and not under other ones. The basis should remain a complete and well-designed clinical programme for the first indication, pre-defined confidence intervals, and the requirement to explore safety for all indications during the life-cycle of the product until such time as the appropriate data set is available.

4. Clinical Safety and Pharmacovigilance (section 5):

- Safety monitoring in the post-approval phase requires identifying the biosimilar medicine. This latter should be branded for traceability purposes, otherwise compound-specific monitoring is not possible if (possibly) several biosimilar products are marketed under a generic name/INN.

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- The risk specification in the application dossier for the biosimilar product has to be based on the experimental data obtained, until this point of time. The drug's own experimental database for safety risk assessment may still be incomplete at the time of evaluation and opinion by the CHMP. In these cases, any remaining safety risks have to be addressed in the SmPC of the product, and can be updated at a later stage depending on the outcome of the post-approval monitoring programme.

5. Immunogenicity testing (section 6):

- It should be stressed that assays for testing antibody formation have to be specific for the biosimilar protein itself. Thus, "generic" assays (or assays developed for the reference compound) may not be adequate. Specificity/selectivity and sensitivity of the assays have to be demonstrated and validated.

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- Long-term testing for antibody formation may only be valid if studies include a sufficient number of patients in order to get a meaningful result (considering an assumed frequency of antibody formation as derived from previous experience with the reference compound). This would be considered part of the risk management plan, covering pre- and post-authorisation evaluation.

SPECIFIC COMMENTS

1. Introduction

1.1 Purpose

Paragraph 1 and 2

A distinction between “comparability” and the data required to demonstrate similarity should be made, and the following paragraph can be changed as follows:

*“Similar biological medicinal products are manufactured and controlled according to their own development. **An extensive comparability** will be required to demonstrate The quality issues relevant for demonstration of ~~comparability~~ **similarity** for similar biological medicinal products containing recombinant DNA-derived proteins are addressed in the ”Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues” (EMA/CHMP/4934/05).*

Comparability will never be possible between a biosimilar medicine and a reference product because comparability should always be based on an assessment of changes strictly related to the same single product within the scope of one defined process for one defined manufacturer.

The objective of a similarity exercise will always be to evaluate whether the inevitable differences between the biosimilar medicine and the reference product will entail safety and efficacy consequences, which will have a negative impact on the benefit/risk balance of the biosimilar medicine.

Paragraph 3

A full quality dossier and demonstration of efficacy and safety is an essential requirement for biosimilar medicines. Quality, safety and efficacy cannot be more closely related and intertwined than with a biological product. In fact, there should be no ambiguity on the needs for **similarity** in terms of efficacy and safety, and the term equivalent should be removed in order to distinguish the need for bioequivalence evaluation on one side (considering what range should be acceptable), and similarity in terms of efficacy and safety on the other side.

Therefore, EBE members suggest that the word “Equivalent” should be removed from Paragraph 3 to read as follow:

“The Marketing Authorisation (MA) application dossier of a biological medicinal product claimed to be similar to a reference product already authorised shall provide a full quality dossier. ~~Equivalent~~ efficacy and safety of the similar biological medicinal product has to be demonstrated...”

Paragraph 4

It seems to EBE members that the term “comparability” is not appropriate and should be replaced by the expression “proof of similarity”.

*“It is recommended that the non-clinical and the clinical overall summary deals with ~~comparability~~ **proof of similarity** issues in separate sections in order to facilitate the regulatory review by cross referencing the appropriate separate sections of the dossier which contain the relevant data...”*

The essence of a biosimilar medicine compared to a traditional generic medicine relates to the difference in active pharmaceutical ingredient (API) between a biosimilar medicine and its reference product. Identity, in the sense of being identical, is not possible in this case. Therefore, “therapeutic equivalence” in the strict sense between a reference product and a product claimed to be similar to the reference product will never be possible, and the sentence “*In certain cases it may be possible to extrapolate therapeutic equivalence shown in one indication to other indications of the reference product*” has to be considered very carefully. In fact extrapolation from one indication to another can only be a recognised scientific approach under very strict principles:

- Extrapolation from one indication to another must remain a case by case approach (the product specific guidelines should address the conditions for the product concerned);
- Extrapolation between the reference product and the biosimilar medicine is not scientifically sound because of the need to properly characterise the biosimilar medicine from a clinical perspective. In view of this, the development of the first indication must be related to a complete and well-designed clinical programme, and extrapolation to another indication has to be included in the corresponding product-specific guidelines with the pre-definition of the confidence intervals around the expected point estimate;
- Safety cannot be extrapolated and any indication;
- Until such time as the necessary data are available, i.e. development data correlated to post-authorisation clinical and pharmacovigilance data, clinical studies to evaluate safety should be undertaken in order to ensure that a proper benefit-risk evaluation is performed on an on-going basis until the appropriate dataset is available; and
- In this respect, a core SmPC approach, based on existing products of the same type on the market, can be considered with a full integration of safety information, and efficacy limited to the demonstrated indication. Product-specific information can be included as it becomes available and validated.

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Paragraph 6

EBE members would suggest amending this Paragraph as below:

*“In case the reference biological product has more than one indication, or, if appropriate, demonstrated separately for each of the claimed indications (i.e. **different patient population, dose**). Justification will depend on...*

2. Scope

In this Section it is listed relevant current and future guidelines pertaining to medicinal products containing biotechnology-derived proteins as active substances that should be read in conjunction with this guideline. EBE members would recommend including in this list also the Guideline on Similar Biological Medicinal Products (CHMP/437/04).

Additionally, it has been noticed that the last bullet point of this Section should read

- *Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (EMA/CHMP/89249/04).*

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3. Non-clinical data

EBE members would suggest that the first paragraph should read: “*Before going into clinical development, non-clinical studies should be performed. These studies should be comparative in nature and should be designed to detect differences in **PK profile, response and safety** between the similar biological product and the reference product and not just the response per se*”.

In vitro studies

Assays have to be designed in order to provide information on the functional properties of the protein compound, rather than the molecular properties. The following paragraph can be written as follows: “*A battery of **functional assays, e.g. receptor-binding studies or cell-based assays, many of which may already be available from quality-related bioassays, should normally be undertaken in order to assess if any differences in reactivity are present and to determine the likely causative factor(s)***”.

In vivo studies

EBE members would suggest that in the list of endpoints to monitor the “**Pharmacokinetic differences to the reference product**” is added.

Non-clinical toxicity studies will never be adequate to reliably detect differences in immune response between the biosimilar and the reference product with sufficient certainty. Nevertheless, such studies are necessary to get preliminary information on significant differences concerning immunogenicity which might be relevant for the design of the following clinical studies. Thus, the paragraph should read:

“*Non-clinical toxicity as determined in at least one repeat dose toxicity study (**with relevant duration based on clinical use**), including toxicokinetic measurements. Toxicokinetic measurements should include determination of antibody titres, cross reactivity and neutralising capacity. The duration of the studies should be sufficiently long to allow detection of relevant differences in toxicity ~~and/or~~ **and to obtain preliminary information on differences in** immune responses between similar biological medicinal product and reference product*”.

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4. Clinical studies

Paragraph 2 and 3

The wording “comparability study” or “comparability exercise” is not appropriate, and should be replaced as follows:

“*It is acknowledged that the manufacturing process will be optimised during development. It is recommended to generate the required clinical data for the **comparative studies supporting the claim of similarity** with **the test product as produced with the final manufacturing process and therefore representing the quality profile of the batches to become commercialised**. Any deviation from this recommendation should be justified and supported by adequate additional data.*

*The clinical **comparative studies supporting the claim of similarity** is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy trial(s) or, in certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for demonstrating **similarity**, according to the following rules*”.

4.1. Pharmacokinetics

Paragraph 1

EBE members would suggest that this paragraph should read:

“Comparative PK studies designed to demonstrate equivalence between the similar biological medicinal product and the reference product with regard to key PK parameters are an essential part of the comparative studies supporting the claim of similarity”

4.1. 4.2. Pharmacodynamic studies

The numbering 4.1 should be reviewed by 4.2.

4.3. Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

Paragraph 5

In order to restrict clinical trials to comparative PK/PD studies, it should not be considered sufficient to accept “at least one PD marker” or “even established as a surrogate marker” if the surrogate marker is not clinically validated with respect to its correlation to clinical efficacy. Thus, the paragraph should read:

*“At least one **clinically validated** PD marker is accepted or even established as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is well known...”*

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4.4. Efficacy trials

EBE members would suggest modifying the first paragraph as follow:

*“Efficacy studies have to be designed to prove equivalence within pre-defined margins. A “better” outcome (compared to the reference product) is not an option for a biosimilar. The patient population selected should be equivalent to the approved indication of the reference product. Usually comparative clinical trials will be necessary to demonstrate ~~therapeutic equivalence similarity~~ between the ~~similar biological~~ **biosimilar medicine** and the reference product. Equivalence margins should be prespecified and justified, primarily on clinical grounds. As for all equivalence trial designs, assay sensitivity (see ICH topic E10) has to be ensured...”*

5. Clinical safety and pharmacovigilance requirements

EBE members propose modifying this section as follow:

*“Even if the efficacy is shown to be comparable, the similar... . Pre-licensing safety data should be obtained in a number of patients sufficient to ~~address the comparability of~~ **compare** the adverse effect profiles of the test and the reference product. Care should be given to compare the type, severity and frequency of the common adverse reactions between the similar biological and the reference biological medicinal product.*

Data from pre-authorisation clinical studies ... post-approval phase including continued benefit-risk assessment.

Identification of the biosimilar medicine is essential for traceability purposes.

The applicant should give a risk specification in the application dossier for the medicinal product under review. ...

...In the PSURs submitted within the first five-year period, the marketing authorisation holder should address reports and any other information on tolerability that he has received. These reports or information must be evaluated and assessed by the marketing authorisation holder in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies. **The specific safety profile of the biosimilar medicine will be addressed in the SmPC of the product”.**

6. Immunogenicity

Consequences of an immune response

It is recommended to add the following sentence:

“The consequences of immunogenicity may vary considerably, ranging from neutral, i.e. irrelevant for therapy, to serious and life-threatening. Therefore, the immunogenicity issue has become a subject of concern in the development and approval of biopharmaceuticals. An immune response to the product may, or may not, have a significant impact on its clinical safety and efficacy. Although only neutralising antibodies directly alter the pharmacodynamic effect, any binding antibody may affect the pharmacokinetics...”.

Principles for evaluation of immunogenicity

EBE members would suggest to add the following information in this guideline:

“Due to the unforeseeable, and potentially serious, consequences of immunogenicity, there is the need for manufacturers of therapeutic proteins (innovators as well as biosimilar manufacturers):

- To assess the immunogenic properties of their protein products during development, as well as**
- To monitor immunogenic events in patients during clinical trials and after approval.**

Assessment of immunogenicity is even more important since of all recombinant therapeutic proteins approved for marketing until now, about 50% have a modified sequence and therefore possess structural differences as compared to the native human protein, and this percentage is expected to rise further in the future.

With biosimilar medicines, the strategy for evaluating immunogenicity should

- 1. Take the available history of the innovator product (the reference product) into account and**
- 2. Include product-specific immunogenicity studies for the respective biosimilar medicine in appropriate clinical trial designs as well as via post-marketing surveillance”.**

Testing

EBE members would prefer to view this section as a “Testing strategy” and would therefore suggest reviewing the title accordingly.

To better reflect this new title, EBE members are proposing additional text:

“Testing strategy

A comparison of immunogenicity of innovative and biosimilar protein products can only be made in comparative clinical trials. In the interest of patient safety, no protein drug can be approved without data on its immunogenic properties obtained in clinical studies of adequate size and duration (e.g., in the case of chronic administration, one-year follow-up data will be required). The patients’ immune system may be influenced by the disease as well as by co-medication; this may lead to the observation that the incidence and clinical phenotype is different for the same product when used in different indications.

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During these studies, the formation of anti-product antibodies has to be analysed carefully with sensitive and compound-specific methods, e.g. enzyme immunoassays, and their correlation with clinical findings has to be investigated. A strategy with a rationale for antibody testing must be available.

The timely availability of these assays to monitor, confirm and characterise immunogenicity in clinical studies is a prerequisite for any clinical program. ELISA-based assays are considered to be state-of-the-art for screening purpose. They should be designed in an appropriate way to be able to detect low-titer and low-affinity antibodies. If antibody formation is observed and confirmed by additional assays, the antibodies have to be characterised carefully in order to assess the impact on the therapy scheme, patient selection, etc. Usually functional assays with the capacity to detect neutralizing effects of the anti-product antibodies need to be available. The nature of these functional assays will depend on the actual drug and the type of drug target intervention. In any case they have to be developed separately for each product.

~~The applicant should present a rationale for the proposed antibody testing strategy. Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies.~~ An assay for neutralising antibodies should be available for further characterisation of antibodies detected by the screening assays. Standard methods and international standards should be used whenever possible. The possible interference of the circulating antigen with the antibody assays should be taken into account. The periodicity and timing of sampling for testing of antibodies should be justified.

*In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies (e.g. **antibodies against the biosimilar medicine and against the endogenous protein, as applicable**) at predetermined intervals will be required. In case of chronic administration, one-year follow up data will be required pre-licensing”.*

In addition to testing for antibodies against the similar medicine, where applicable, testing for antibodies against an endogenous protein should be systematically requested (e.g. anti-erythropoietin antibodies should be tested in clinical trials for erythropoietin).

EBE – October 2005
