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Evaluation of Medicines for Human Use

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

**GUIDELINE ON
SIMILAR BIOLOGICAL MEDICINAL PRODUCTS**

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1. INTRODUCTION

1.1 REGULATORY FRAMEWORK

A company may choose to develop a new biological medicinal product claimed to be “similar” to a reference medicinal product, which has been granted a marketing authorisation in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83, as amended. For this scenario, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive¹ lays down the requirements for the Marketing Authorisation Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the Community.

1.2 SCOPE

The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (see Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC), e.g.: medicinal products containing biotechnology-derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies, etc.

The CHMP guidelines addressing the planning and conduct of comparability studies should always be read in conjunction with relevant legislative and administrative provisions in force in the EU.

1.3 NEED TO ISSUE GUIDANCE ON THIS EMERGING ISSUE

The applicants of similar biological medicinal products, who have applied for scientific advice from the CHMP, expressed the need for specific guidance.

The advances as well as the limitations of methods and techniques available today for the full characterization of such medicinal products have already prompted the CHMP to initiate a number of specific guidelines relevant to quality, non-clinical and clinical issues, to be addressed within the development programs of similar biological medicinal products.

1.4 PURPOSE

Section 4, Part II, Annex I to Directive 2001/83/EC states that *‘the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency’*.

The purpose of this guideline is:

- To introduce the concept of similar biological medicinal products;
- To outline the basic principles to be applied;
- To provide applicants with a ‘user guide’, showing where to find relevant scientific information in the various CHMP guidelines, in order to substantiate the claim of similarity.

In any case, companies developing similar biological medicinal products are invited to contact the Agency to obtain further advice on their development.

2. BASIC PRINCIPLES

2.1 APPLICATION OF “SIMILAR BIOLOGICAL MEDICINAL PRODUCTS” APPROACH

In principle, the concept of a “similar biological medicinal product” is applicable to any biological medicinal product. However, in practice, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.

¹ As amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46 and Directive 2004/27/EC, OJ L136, 30.4.2004, p.34.

Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be ‘minor’ in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.

Therefore:

- The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived medicinal products. Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products. The “similar biological medicinal products” approach, based on a comparability exercise, will then have to be followed.
- Comparability exercises to demonstrate similarity are more likely to be applied to highly purified products, which can be thoroughly characterised (such as some biotechnology-derived medicinal products).
- The ‘similar biological medicinal product’ approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterise, such as biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained.
- Whether a medicinal product would be acceptable using the ‘similar biological medicinal product’ approach depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences.
- The similar biological medicinal product shall, with regard to the quality data, fulfill all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC and satisfy the technical requirements of the monographs of the European Pharmacopoeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines
- The requirements to demonstrate safety and efficacy of similar biological medicinal products have to comply with the data requirements laid down in Annex I to Directive 2001/83/EC. General technical and product-class specific provisions are addressed in EMEA/CHMP guidelines (see Section 3.2). For situations where product-class specific guidance is not available, applicants are encouraged to seek scientific advice from EU Regulatory Authorities.
- It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.

2.2 CHOICE OF REFERENCE PRODUCT

The chosen reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

The chosen reference medicinal product, defined on the basis of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies during the development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions.

Data generated from comparability studies with medicinal products authorised outside the Community may only provide supportive information.

The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, a medicinal product containing interferon alfa-2a manufactured by Company X claiming to be similar to another biological medicinal product should refer to a reference medicinal product containing as its active substance interferon alfa-2a. Therefore, a medicinal product containing interferon alfa-2b could not be considered as the reference medicinal product.

The pharmaceutical form, strength and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product. When the pharmaceutical form, the strength or the route of administration is not the same; additional data in the context of the comparability exercise should be provided. Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis.

Consultation with the EMEA is highly recommended to discuss all those issues.

3. RELEVANT GUIDELINES

As stated above, the CHMP has or may develop additional guidance documents addressing both the quality, non-clinical and clinical aspects for the development of similar biological medicinal products. Product-class specific guidance documents on pre-clinical and clinical studies to be conducted for the development of defined similar biological medicinal products will be made progressively available.

It should be noted that the scientific principles described in quality and non-clinical/clinical guidelines applicable to similar biological medicinal products containing biotechnology-derived proteins, as active substance may also be useful when considering non biotechnology-derived biological medicinal products.

3.1 GUIDELINES APPLICABLE TO ALL SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

CHMP guidelines are available at the following address on the EMEA website:
<http://www.emea.eu.int/index/indexh1.htm>

While developing a similar biological medicinal product and carrying out the comparability exercise to demonstrate that this product is similar to another one already authorised in the EU, some existing CHMP guidelines may be relevant and should therefore be taken into account. For example:

- CPMP/BWP/328/99 Development Pharmaceuticals for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceuticals (CPMP/QWP/155/96)
- Topic Q5C, Step 4 Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (CPMP/ICH/138/95 - adopted Dec. 95)
- Topic Q6B, Step 4 Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96 - Adopted March 99)
- ICH Topic S6, Step 4 Note for Preclinical Safety Evaluation of Biotechnology-Derived Products (CPMP/ICH/302/95 - adopted Sept. 97)

3.2 BIOLOGICAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE

- In addition to this guideline, the CHMP is developing further guidelines on Similar Biological Medicinal Products (see CHMP monthly report, May 2005), e.g.:
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Quality issues (EMEA/CHMP/BWP/49348/2005).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/2005).

- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues-guidance on biosimilar medicinal products containing recombinant human insulin (EMEA/CHMP/32775/2005).
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues-guidance on biosimilar medicinal products containing somatropin (EMEA/CHMP/94528/2005).

Additional product-class specific annexes are envisaged to provide guidance for products containing rG-CSF and epoetin and others as the need arises and will be made available in the EMEA website.

These guidelines are available at the following location on the EMEA website:

<http://www.emea.eu.int/index/indexh1.htm> (Guidance Documents / Biosimilar Products)

The current guidelines, relevant to comparability and similar biological medicinal products will be complemented by the above guidelines for aspects concerning similar biological medicinal products. In addition, the quality guideline (CPMP/BWP/3207/00) will be replaced by ICH Q5E for aspects concerning quality changes to the manufacturing processes of biotechnological/biological products by:

- The “Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance – Quality issues (CPMP/BWP/3207/00)”.
- The “Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance - Non-clinical and clinical issues (CPMP/Ad-Hoc group on (non)-clinical comparability of biotechnology products/3097/02)”.

3.3 IMMUNOLOGICALS SUCH AS VACCINES AND ALLERGENS

Vaccines are complex biological medicinal products. Currently, it seems unlikely that these products may be thoroughly characterised at a molecular level. Consequently, vaccines have to be considered on a case-by-case basis. Applicants should take appropriate advice from the EU Regulatory Authorities.

Allergen products are similarly complex and the same approach should be taken.

In addition to the CHMP guidelines applicable to all biological medicinal products (listed in paragraph 2 of this document), the following guidelines should be taken into consideration.

The CHMP guidelines addressing the quality, non-clinical and clinical aspects of immunological such as vaccines are the following:

- CPMP/BWP/477/97 Note for guidance on Pharmaceutical and Biological Aspects of Combined Vaccines, (CPMP adopted Jul. 98).
- CPMP/BWP/2490/00 Note for Guidance on Cell Culture Inactivated Influenza Vaccines (Adopted by CPMP January 2002) - Annex to Note for Guidance on Harmonisation of requirements for Influenza Vaccines CPMP/BWP/214/96
- CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP adopted March 97)
- CPMP/BWP/2289/01 Points to Consider on the Development of Live Attenuated Influenza Vaccines (CPMP Adopted, February 2003)
- CPMP/BWP/243/96 Note for Guidance on Allergen Products (CPMP adopted March.96)
- CPMP/EWP/463/97 Note for guidance on Clinical Evaluation of New Vaccines (CPMP adopted 19 May 99)

These guidelines are available at the following address on the EMEA website:
<http://www.emea.eu.int/htms/human/bwp/bwffin.htm>

Draft guidance documents may also be relevant and may be found at the following address on the EMEA website: <http://www.emea.eu.int/htms/human/bwp/bwpdraft.htm>

3.4 BLOOD OR PLASMA-DERIVED PRODUCTS AND THEIR RECOMBINANT ALTERNATIVES

The BWP and BPWG guidelines listed below should be taken into consideration, in addition to the applicable CHMP guidelines (Section 3.1 and 3.2).

In view of the complex and variable physico-chemical, biological and functional characteristics of the products listed in the BPWG guidelines mentioned below, it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described in these BPWG guidelines for “new products”.

For quality issues:

- CPMP/BWP/269/95 Rev.3 Note for guidance on Plasma -Derived Medicinal Products (CPMP adopted Jan. 2001).

This guideline is available at the following address on the EMEA website:

<http://www.emea.eu.int/htms/human/bwp/bwpfin.htm>

For non-clinical and clinical considerations:

- CPMP/BPWG/283/00 Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular use (Adopted July 2002)
- CPMP/BPWG/2220/99 Note for Guidance on the Clinical Investigation of Plasma derived Antithrombin Products (Adopted January 2002)
- CPMP/BPWG/198/95 Rev. 1 Note for Guidance on the Clinical Investigation of Human Plasma Derived Factor VIII and IX Products (Adopted October 2000)
- CPMP/BPWG/1561/99 Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products (Adopted October 2000)
- CPMP/BPWG/388/95 Rev. 1 Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (Adopted June 2000)
- CPMP/BPWG/575/99 Note for Guidance on the Clinical Investigation of Human Anti-D Immunoglobulin for Intravenous and/or Intramuscular Use (Adopted June 2000)

These documents are available at the following address on the EMEA website:

<http://www.emea.eu.int/htms/human/bpwg/bpwgfin.htm>

Draft guidance documents may also be relevant and may be found at the following address on the EMEA website: <http://www.emea.eu.int/htms/human/bpwg/bpwgdraft.htm>

3.5 OTHER BIOLOGICAL MEDICINAL PRODUCTS

Other types of biological medicinal products exist, such as gene or cell therapy medicinal products. These products are of a complex nature and will be considered in the future in light of the scientific knowledge and regulatory experience gained at the time.