2. BASIC PRINCIPLES

2.1 Application of 'Biosimilar' 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.

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 'biosimilar' approach, based on a comparability exercise, will then have to be followed.
- Comparability exercises to demonstrate biosimilarity are more likely to be applied to highly purified products, which can be thoroughly characterised (such as some biotechnology-derived medicinal products).
- Although not legally forbidden, the 'biosimilar' 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 (such as gene and cell therapy products).
- Whether a medicinal product would be acceptable using the 'biosimilar' approach depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences.
- The requirements to demonstrate safety and efficacy are essentially product-class specific. Therefore, the non-clinical/clinical data package is determined on a case-by-case basis, for situations where product-class specific guidance has not been defined.
- 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 biosimilar 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 product given to the patient should be clearly identified.

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2.2 Choice of Reference Product

A "reference medicinal product" is a medicinal product authorised in the EEA, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

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 same reference product 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.

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 or the strength or the route of administration are not the same, the results of appropriate non-clinical/clinical trials must be provided in order to demonstrate the safety/efficacy of the similar biological medicinal product. 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.

3. RELEVANT GUIDELINES

As stated above, the CHMP has or may develop additional guidance documents addressing both the quality, non-clinical and clinical aspects of comparability relevant to biotechnology-derived medicinal products and to other types 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 Pharmaceutics for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceutics (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)

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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)

Additional class-product specific guidelines are progressively developed from the CHMP and will be made available in the EMEA website.

3.2 Biological products containing biotechnology-derived proteins as active substance

The CHMP has developed and published two guidelines addressing the specific comparability aspects of biotechnology-derived medicinal products. The two guidelines address respectively, the quality issues of comparability and the non-clinical and clinical issues associated with this kind of comparability exercise. These two guidelines are:

- The "Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance – Quality issues (CPMP/BWP/3207/00)".

  This guideline is available at the following address on the EMEA website: http://www.emea.eu.int/pdfs/human/bwp/320700en.pdf

- 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)".

  This guideline is available at the following address on the EMEA website: http://www.emea.eu.int/htms/human/bwp/bwpfin.htm

These guidelines initially addressing the comparability exercise needed both for changes in the manufacturing process of a given products and for the demonstration of the similar nature of a similar biological medicinal product to an authorised reference medicinal product are regularly revised as appropriate to accommodate upcoming changes in scientific knowledge and legal framework.

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 will 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)

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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/bwpfin.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 an original (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

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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.

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資料2

European Medicines Agency
Evaluation of Medicines for Human Use

Doc Ref: EMEA/CHMP/BWP/49348/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES

DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY	September 2004 to February 2005
TRANSMISSION TO CHMP	February 2005
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RELEASE FOR CONSULTATION	March 2005
DEADLINE FOR COMMENTS	30 June 2005

Note:
Any comments to this guideline should be sent to the EMEA (Biologics Working Party Secretariat), Fax: +44 20 7418 8545 or E-mail: Linda.Olsson@emea.eu.int by 30 June 2005.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.eu.int http://www.emea.eu.int
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SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES

1. Introduction

1.1 Purpose

A company may choose to develop a new biological medicinal product claimed to be similar (Similar Biological Medicinal Product) in terms of Quality, Safety and Efficacy to an original, reference medicinal product which has been granted a marketing authorisation in the Community (see Guideline on Similar Biological Medicinal Products, CHMP/437/04).

Similar Biological Medicinal Products are manufactured and controlled according to their own development, taking into account relevant and up-to-date information, such as manufacturing processes, product characteristics, stability and comparability data.

In most cases, limited comparison can be made against the official data, e.g. pharmacopoeial monographs or against other published scientific data. However, such comparisons at the level of both active substance and finished product are not sufficient to establish all aspects pertinent to the evaluation of biosimilarity. Consequently, an extensive comparability exercise will be required to demonstrate that the biosimilar and reference products have similar profiles in terms of quality, safety and efficacy.

Based on the comparability approach and when supported by sufficiently sensitive analytical systems, the demonstration of comparability at the quality level may connect the biosimilar product to the nonclinical and clinical data previously generated with the reference product.

1.2. Regulatory framework

A full quality dossier (CTD Module 3) is required as detailed in current legislation and this should be supplemented by the demonstration of comparability, as discussed in this guideline. Applicants should note that the comparability exercise for a biosimilar product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier and should be dealt with separately when presenting the data. It is recommended that the Quality Overall Summary also deals with comparability issues in separate sections in order to facilitate review, cross referencing the appropriate separate sections of the dossier which contain the relevant data. It may also be helpful to include any considerations of comparability during development of the biosimilar product in a similar way.

This guideline should be read in conjunction with all relevant current and future guidelines pertaining to medicinal products containing biotechnology-derived proteins as active substance, and in conjunction with Part II of the Annex I of Directive 2001/83/EC, as amended.

1.3. Scope

This guideline addresses quality issues during demonstration of comparability for Similar Biological Medicinal Products (biosimilar products) containing recombinant DNA-derived proteins. As a consequence, the principles adopted and explained in this document should apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). For other situations see Guideline on Similar Biological Medicinal Products, CHMP/437/04.

This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e. changes during development and post-authorisation), as addressed by ICH Q5E.

2. Manufacturing process of a biosimilar medicinal product

The biosimilar product is defined by its own specific manufacturing process for both active substance and medicinal product. This process should be developed and optimised taking into account state-of-the-art information on manufacturing processes (i.e. expression system / cell substrate, culture, purification, viral safety, etc.) and consequences on product characteristics.

It is recognised that each medicinal product is defined by the molecular composition of the active substance resulting from its process, which may introduce its own process related impurities. Consequently, the biosimilar product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/impurities), and ii) related to its process. It is the duty of the Applicant to demonstrate the consistency and robustness of his own process according to existing guidelines.

Formulation studies should be considered in the course of the development of a suitable dosage form, even if excipients are qualitatively and quantitatively the same as the reference product. These studies should demonstrate the suitability of the proposed formulation with regards to stability, compatibility (i.e. with excipients, diluents and packaging materials), and integrity of the active substance (both biologically and physico-chemically) for its intended medicinal use.

As is the case for any biotechnology-derived medicinal product, a comparability exercise (as described in ICH Q5E) should be considered when a change is introduced into the manufacturing process (active substance and finished product) during development. For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified and addressed separately from the comparability exercise intended to demonstrate biosimilarity to the reference product.

Although it is acknowledged that the manufacturing process will be optimised during development, it is advisable to generate the required clinical data for the comparability study with product produced with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.

3. Comparability exercise for demonstrating biosimilarity

This section addresses the points to be considered in the demonstration of similarity for a biosimilar product versus that of a reference product.

Although quality aspects of a biosimilar product are a fundamental element in the comparability exercise versus the reference medicinal product, quality aspects should always be considered with regard to any implications for Safety and Efficacy. A stepwise approach should be undertaken to justify any differences in the quality attributes of the biosimilar versus the reference product in order to make a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.

It is not expected that the quality attributes in the biosimilar and reference medicinal products will be identical. For example, minor structural differences in the active substance, such as variability in post-translational modifications may be acceptable, however, must be justified. The impurity profile in the product should be fully justified and would be considered on a case-by-case basis, and supported by the comparability exercise for quality attributes in relation to safety and efficacy. Therefore,

differences in impurity profiles and significant differences in product related substances may have consequences with regard to the amount of data which may be required in order to make satisfactory justification of the safety and efficacy of the biosimilar product.

3.1. Reference product for biosimilar medicinal products

Comparability of the biosimilar medicinal product with the chosen reference product should be addressed for both the medicinal product and the active substance in the medicinal product.

3.1.1. Reference Medicinal Product

The reference medicinal product should be authorised in the European Union. Although the biosimilarity exercise can be facilitated when the pharmaceutical form, formulation, strength etc. of the biosimilar product are the same as the reference medicinal product, other approaches may be considered by the applicant. In any case, a clear scientific justification of the criteria followed to select the reference medicinal product should be provided, with specific attention to its critical parameters and quality attributes. The same reference medicinal product should be used for all three parts of the dossier (i.e. Quality, Safety and Efficacy).

The brand name, pharmaceutical form, formulation and strength of the reference medicinal product used in the comparability exercise should be clearly identified. The effect of sample age of the reference product on the results of the comparability exercise should be adequately addressed, where appropriate.

3.1.2. Reference Active Substance

The comparison of the biosimilar active substance to a publicly available standard as a reference (i.e. Ph.Eur., WHO, etc.) is not sufficient to demonstrate biosimilarity of the active substance since this material may not have known and defined safety and efficacy profiles. In addition, the biosimilar manufacturer generally does not have access to the originator active substance, and cannot directly compare his active substance to the one used in the originator's medicinal product.

Nevertheless, the biosimilar manufacturer must demonstrate, using state of the art analytical methods that the active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product. In certain situations, the analytical tools used for characterisation may not be capable of directly comparing the biosimilar active substance versus the active substance present in the reference medicinal product. In these situations, the Applicant should use various approaches to obtain representative reference active substance derived from the reference medicinal product in order to perform the comparative analysis at the active substance level. This approach should be appropriately validated in order to demonstrate the suitability of the sample preparation process, and should include the comparison of the biosimilar active substance with active substance material derived from the reference and the biosimilar medicinal products.

3.2. Analytical methods for biosimilar medicinal products

Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference medicinal products in parallel at both the active substance and the medicinal product levels to demonstrate with a high level of assurance that the quality of the biosimilar product is comparable to the reference medicinal product.

3.2.1. Analytical considerations

- Suitability of available analytical methods

Given the complexity of the molecule and its inherent heterogeneity, the set of analytical techniques should represent the state-of-the-art and should be selected by the manufacturer as being able to detect any slight differences in the characteristics of the biotechnology-derived product. It is the duty of the manufacturer to demonstrate that the selected methods used in the comparability exercise would be able to detect differences in all aspects pertinent to the evaluation of quality.

- Validation of analytical methods

Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability. Before entering the clinical trial(s) needed for comparability purposes, release tests should be validated in accordance with the ICH Harmonised Tripartite Guidelines "Validation of Analytical Procedures: Definitions and Terminology" and "Validation of Analytical Procedures: Methodology".

If available, primary standards (e.g., from Ph. Eur., WHO, etc.) should be used for method qualification and validation.

3.2.2. Physicochemical properties

The physicochemical comparison comprises the evaluation of physicochemical parameters and the structural identification of product-related substances and impurities, including the determination of the degradation pathways by performing accelerated stability studies. A physicochemical characterisation program should include a determination of the composition, physical properties, primary and higher order structures of the active substance of the biosimilar product. An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process, therefore, the biosimilar product can contain a mixture of anticipated post-translationally modified forms.

3.2.3. Biological activity

The comparability exercise should include an assessment of the biological properties of the similar biological medicinal product and the reference medicinal product. Biological assays using different approaches to measure the biological activity should be considered as appropriate (i.e. depending on the biological properties of the product). The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. These assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable.

3.2.4. Purity and impurities

The purity and impurity profiles of the active substance and medicinal product should be assessed both qualitatively and quantitatively by a combination of analytical procedures for both reference and biosimilar products. It is acknowledged that the manufacturer developing biosimilar products would normally not have access to all necessary information that could allow an exhaustive comparison with the reference medicinal product. Nevertheless the level of detail must be such that firm conclusions on the purity and impurity profiles can be made.

The product-related substances and impurities in the biosimilar product should be identified and compared to the originator product using state-of-the-art technologies. Additionally, information based on the analysis of samples stored under accelerated conditions, inducing selective degradation (e.g., oxidation, dimerisation) should be used for identification. Comparison of product-related

substances, and of product-related impurities should be based on specific degradation pathways and potential post-translational modifications of the individual proteins. Additional accelerated stability studies of the originator and of the biosimilar product should be used to further define and compare the degradation pathways.

Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, downstream impurities, etc.) are expected to differ qualitatively from one process to another, and therefore, the qualitative comparison of these parameters may not be relevant in the comparability exercise. Nevertheless, state-of-the-art analytical technologies following existing guidelines and compendial requirements should be applied, and the impact of these process-related impurities should be confirmed by appropriate studies (including non-clinical and/or clinical studies).

4. Specifications

As for any biotechnology-derived product, the selection of tests to be included in the specifications is product specific and should be defined as described in ICH Q6B: *Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological.* The rationale used to establish the proposed range of acceptance criteria should be described. Each acceptance criteria should be established and justified based on data obtained from lots used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data and data obtained from the comparability exercise (quality, safety and efficacy).

The setting of specifications should be supported by global reasoning based on the Applicant's experience of the biosimilar product (quality, safety and efficacy) and his own experimental results obtained by testing the reference medicinal product. These data should demonstrate, whenever possible, that the limits set for a given test are not wider than the range of variability of the representative reference material, unless justified.

資料3

European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 May 2005
EMEA/CHMP/42832/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES

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Note:

Any comments to this Guideline should be sent to the EMEA BMWP Secretariat by e-mail:

Denisa.dechiara@emea.eu.int or by fax: +44 20 74 18 86 13 by the end of October 2005

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int
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1. Introduction

1.1 Purpose

A company may choose to develop a new biological medicinal product claimed to be similar (similar biological medicinal product) in terms of quality, safety and efficacy to an original/reference product that has been granted a marketing authorisation in the Community (see Guideline on similar biological medicinal products, CHMP/437/04).

Similar biological medicinal products are manufactured and controlled according to their own development. An extensive comparability exercise will be required to demonstrate that the similar biological and reference products have similar profiles in terms of quality, safety and efficacy. The quality issues relevant for demonstration of comparability 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" (EMEA/CHMP/4934/05).

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. The principles for this exercise are laid down in this guideline. Product class specific annexes will supplement this guideline for specific products classes where a need has been or will be identified.

It is recommended that the non-clinical and the clinical overall summary deals with comparability 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 same reference product should be used for all three parts of the dossier (i.e. quality. safety and efficacy aspects).

In case the reference biological product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar have to be justified or, if appropriate, demonstrated separately for each of the claimed indications. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed. In certain cases it may be possible to extrapolate therapeutic equivalence shown in one induction to other indications of the reference product.

In any case, the company should justify the approach taken during the development of the product and might want to contact the EMEA before starting the development for scientific and regulatory advice.

2. Scope

This guideline addresses the general principles for the non-clinical and clinical development and assessment of the marketing authorisation applications of similar biological medicinal products containing recombinant proteins as active substance(s). This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e. changes during development and post-authorisation).

This guideline should be read in conjunction with all relevant current and future guidelines pertaining to medicinal products containing biotechnology-derived proteins as active substance, and in conjunction with Part II of the Annex I of Directive 2001/83/EC, as amended, especially.

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMEA/CHMP/4924/05)

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- Guideline on similar biological products (CHMP/437/04) ICH topic S6 - Note for guidance on Non-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (EMEA/CHMP/89249/04/in pre)

3. Non-clinical data

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 response between the similar biological product and the reference product and not just the response *per se*.

It is important to note that design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physicochemical and biological characterisation studies should be reviewed from the point-of-view of potential impact on efficacy and safety. Relevant guidance documents, notably the "Note for guidance on Non-clinical safety evaluation of biotechnology derived pharmaceuticals" (CPMP/ICH/302/95), should be taken into consideration.

Ongoing consideration should be given to the use of emerging technologies. (For example: *In vitro* techniques such as e.g. 'real-time' binding assays may prove useful. *In vivo*, the developing genomic/proteomic microarray sciences may, in the future, present opportunities to detect minor changes in biological response to pharmacologically active substances).

The following approach may be considered and should be tailored to the specific product concerned on a case-by-case basis. The approach taken will need to be fully justified in the non-clinical overview.

In vitro studies:
A battery of 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:
Animal studies should be designed to maximise the information obtained and to compare reference and similar biological medicinal products intended to be used in the clinical trials. Such studies should be performed in a species known to be relevant and employ state of the art technology. Where the model allows, consideration should be given to monitoring a number of endpoints such as:

- Pharmacodynamic effect/activity relevant to the clinical application.
- Non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements. Toxicokinetic measurements should include determination of antibody titres, cross reactivity and neutralizing capacity. The duration of the studies should be sufficiently long to allow detection of relevant differences in toxicity and/or immune responses between similar biological medicinal product and reference product.

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- If there are specific safety concerns, these might be addressed by including relevant observations (i.e. local tolerance) in the same repeat dose toxicity study.

4. Clinical studies

The requirements depend on the type of the biological medicinal product and the claimed therapeutic indication(s). Available disease specific guidelines should be followed when appropriate.

It is acknowledged that the manufacturing process will be optimised during development. It is recommended to generate the required clinical data for the comparability study with 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 comparability exercise 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 therapeutical equivalence, according to the following rules.

4.1. Pharmacokinetics

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 comparability exercise.

Specific considerations related to the inherent characteristics of proteins are described in the Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (EMEACHMP/89249/2004/in prep) and they should be taken into account.

The design of comparative PK studies should not necessarily mimic that of the standard "equivalence" design (CHMP/EWP/QWP/1401/98), since similarity in terms of absorption/bioavailability is not the only parameter of interest. In fact, differences in elimination characteristics between products e.g. clearance and elimination half-life should be explored.

The choice of the design for single dose studies, steady-state studies, or repeated determination of PK parameters with a treatment period in between should be justified by the applicant. The ordinary crossover design is not appropriate for therapeutic proteins with a long half-life, e.g. therapeutic antibodies and pegylated proteins, or for proteins for which formation of anti-drug antibodies is likely. The acceptance range to conclude equivalence with respect to any pharmacokinetic parameter should be based on clinical judgement, taking into consideration all available efficacy and safety information on the reference and test products. Hence, the criteria used in standard equivalence studies, initially developed for chemically derived products may not be appropriate and the equivalence limits should be defined and justified prior to conducting the study.

4.1. Pharmacodynamic studies

The pharmacodynamic (PD) markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. The pharmacodynamic effect of the test and the reference products should be compared in a population where the possible differences can best be observed. The design and duration of the studies must be justified. Combined PK / PD studies may provide useful information on the relationship between exposure and effect. The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful.

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

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Normally comparative clinical trials are required for the demonstration of equivalent efficacy. In certain cases, however comparative PK/PD studies between the similar biological medicinal product and the reference product may be sufficient to demonstrate equivalence, provided that all the following conditions are met:

- The PK of the reference product, including detailed knowledge of the relevant biological barriers, are well characterised.
- There is sufficient knowledge of the pharmacodynamic properties of the reference product, including binding to its target receptor(s) and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.
- The relationship between dose/exposure and response/efficacy of the reference product (the therapeutic "concentration-response" curve) is reasonably well characterised.
- At least one 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. A PD marker may be considered a surrogate marker for efficacy if therapy-induced changes of that marker can explain changes in clinical outcome to a large extent. Examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), and early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons. The choice of the surrogate marker for use in PK/PD studies should be thoroughly justified.

If PK/PD studies are used to demonstrate similarity of the biological medicinal products, care should be taken to investigate a reasonable dose range to demonstrate assay sensitivity (see ICH topic E10).

The margins defining equivalence of PK and PD parameters must be defined a priori and justified.

4.4. Efficacy trials

Usually comparative clinical trials will be necessary to demonstrate therapeutic equivalence between the similar biological and the reference product. Equivalence margins should be pre-specified and justified, primarily on clinical grounds. As for all equivalence trial designs, assay sensitivity (see ICH topic E10) has to be ensured.

If an equivalence trial design is not feasible, other designs should be explored and their use discussed with the competent authorities.

5. Clinical safety and pharmacovigilance requirements

Even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a different safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Pre-licensing safety data should be obtained in a number of patients sufficient to address the comparability of 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 products.

Data from pre-authorisation clinical studies normally are insufficient to identify all differences. Therefore, clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.

The applicant should give a risk specification in the application dossier for the medicinal product under review. This includes a description of possible safety issues related to tolerability of the medicinal product that may result from a manufacturing process different from that of the originator.

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Within the authorisation procedure the applicant should present a pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. Pharmacovigilance systems (as defined in the current EU legislation) and procedures (including traceability as described in the current EU guidelines) to achieve this monitoring should be in place when a marketing authorisation is granted. A specific risk management plan is required in situations when there is a safety signal in pre-licensing non-clinical or clinical studies or when safety problems have been encountered with other products of the same class.

The compliance of the marketing authorisation holder with commitments (where appropriate) and their pharmacovigilance obligations will be closely monitored.

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.

6. Immunogenicity

Factors affecting immunogenicity

For many proteins and peptides, a number of patients develop clinically relevant anti-drug antibodies. The immune response against therapeutic proteins differs between products since the immunogenic potential is influenced by many factors, such as the nature of the active substance, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and target patient population. The patient-related factors may have a genetic basis, e.g. lack of tolerance to the normal endogenous protein, or acquired, such as immunosuppression due to the disease or its concomitant medication. There is considerable inter-individual variability in antibody response in terms of different antibody classes, affinities, and specificities Thus, data should be collected from a sufficient number of patients to characterise the variability in antibody response.

Consequences of an immune response

An immune response to the product may 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. Thus, an altered effect of the product due to anti-drug antibody formation might be a composite of both pharmacokinetic and pharmacological changes. Antibody formation can cause increased or decreased clearance of the therapeutic protein, although the former effect is the most common.

Principles for evaluation of immunogenicity

The immunogenicity of a similar biological medicinal product must always be investigated. Normally an antibody response in humans cannot be predicted from animal studies. The assessment of immunogenicity requires an optimal antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects. It is important to consider the risk of immunogenicity in different therapeutic indications separately.

Testing

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

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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 at predetermined intervals will be required. In case of chronic administration, one-year follow up data will be required pre-licensing.

Evaluation of the clinical significance of the observed immune response

If a different immune response to the product is observed as compared to the innovator product, further analyses to characterise the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required. Special consideration should be given to those products where there is a chance that the immune response could affect the endogenous protein and its unique biological function. Antibody testing has to be integrated to all clinical trials. The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. The sponsor needs to discuss possibilities to stimulate the reporting of relevant adverse events, including events related to loss of efficacy.

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