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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**GUIDELINE ON COMPARABILITY OF MEDICINAL PRODUCTS
CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE
SUBSTANCE**

NON-CLINICAL AND CLINICAL ISSUES

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1. INTRODUCTION

This document should be read in conjunction with the “Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance – quality issues (CPMP/BWP/3207/00)”. It does not address other biological medicinal products. It should be read in conjunction with Part II of the Annex I of Directive 2001/83/EC, as amended (Commission Directive 2003/63/EC of 25 June 2003) and current and future guidelines, especially those on:

- ICH topic S6 - Note for guidance on Pre-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)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)
- Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00)
- Note for guidance on the clinical investigation of recombinant Factor VIII and Factor IX products (CPMP/BPWG/1561/99)

2. BACKGROUND

In the “Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active substance – quality issues (CPMP/BWP/3207/00)” two situations are indicated in which comparability might become an issue:

- When a change is introduced in the manufacturing process of a given product (either before the granting of a marketing authorisation or after the granting of a marketing authorisation [variation procedure]).
- When a product is claimed to be similar to another one already authorised in the EU after the expiry of the data protection period (new application procedure).

In either case the company will have to demonstrate or justify that the ‘new’ and ‘original/reference’ products have similar profiles in terms of Quality, Safety and Efficacy. This might be a sequential process, beginning with quality studies (partial or comprehensive) and supported, as necessary, by non-clinical and/or clinical bridging studies.

The purpose of this document is to explore which non-clinical and clinical data will be required in these situations. The data requirements and timing of submission of these data will have to be judged on a case by case basis and will be guided by:

- The extent to which the product may be characterised
- The nature of the changes in the ‘new’ product compared to the ‘original/reference’ product
- The observed/potential differences between the two products
- The clinical experience pertaining to the particular class of products

In addition when a change is introduced during the development of the product, i.e. before authorisation, the type and extent of additional non-clinical and/or clinical data will depend on the stage of the development.

3. CHANGE IN THE MANUFACTURING PROCESS OF A GIVEN PRODUCT

In the guideline mentioned above, situations are indicated when, due to a change in the manufacturing process of a given product¹, an effect on efficacy and/or safety might be expected or cannot be ruled out (see paragraph 2.2 in the “Guideline on comparability of medicinal products containing biotechnology derived proteins as active substance – quality issues” Ref. CPMP/BWP/3207/00). It is assumed that the product’s physico-chemical properties and *in vitro/in vivo* biological activity are well characterised according to state of the art methods, but that these data are insufficient to exclude relevant changes in clinical efficacy and safety.

This document will mainly focus on the kind of non-clinical and/or human data needed in those cases. It should be remembered, however, that, in all situations, the company should justify that the change in the manufacturing process will not affect efficacy and/or safety of the product and that the data underpinning such justification will be assessed.

If a modification of the product is detected during the comparability exercise it may indicate the need for further pre-clinical and/or clinical data.

Due to lack of experience and taking into consideration that this document gives general guidance it should be recognised that the product-specific data requirements will have to be judged on a case by case basis.

Changes to the conditions of manufacture may alter the profile and ratio of impurities, i.e. process and product related impurities, but may also modify the nature and composition of product-related substances. The biological impact of these changes should be considered prior to administration of the product to man.

3.1 General considerations

In this section, issues are mentioned that should be considered when drafting and justifying a development plan to address the efficacy and safety of the (possibly) changed product. Depending on the product and the (anticipated) change, the data package may consist of non-clinical or clinical data or a combination. Applications should be accompanied by an assessment of the potential impact of the variation on efficacy and safety, the rationale behind the development plan should be outlined and justified.

3.1.1 Non-clinical considerations

Data from non-clinical studies can provide useful pointers to potential therapeutic differences in the biological properties of a ‘varied’ version of a product compared with the ‘original/reference’ product. In some cases it may be appropriate to undertake few or even no non-clinical studies, but in other situations a more detailed evaluation may be helpful. It is important to note that safety issues require a clear understanding of the product characteristics in order to design suitable study protocols. Results from the physicochemical characterisation studies should be reviewed from the point-of-view of potential impact on efficacy and safety (e.g. *in vitro/in vivo* biological activity, metabolism, kinetics, immunogenicity etc...). The methods chosen to detect heterogeneity between the “varied” and “original/reference” products should be described. Sufficient information, and cross-referencing to other sections,

¹ In the document when the term ‘product’ is used without qualifiers, it is intended to signify intermediates, active substance and/or finished product.

should be supplied in the non-clinical section to justify the approach taken in subsequent studies.

Non-clinical studies should be comparative in nature and may be used to highlight differences between the ‘varied’ and ‘original/reference’ products. Such studies may have a useful role in the preliminary assessment of safety at one or more points in the development process, thus enabling clinical studies, if needed, to be undertaken with greater confidence. The following approach may be considered and should be tailored to the specific product concerned on a case-by-case basis.

In vitro studies: A battery of receptor-binding studies, many of which may already be available from quality-related bioassays, should normally be undertaken in order to assess if any alterations in reactivity have occurred and to determine the likely causative factor(s).

In vivo studies: If there are specific uncertainties or concerns regarding safety *in vivo* studies in one or more suitable animal models may be considered. Greater reliance would be placed on results from studies in a species shown for the ‘original/reference’ product to be a good model for man. Animal studies should be designed to maximise the information obtained and to compare ‘original/reference’ and ‘varied’ products in the final formulation. In the general case and where the model allows, consideration should be given to monitoring a number of endpoints such as:

- a) Changes in pharmacodynamic parameters, e.g. duration of action.
- b) Changes in pharmacokinetic parameters, e.g. clearance.
- c) The immune response, e.g. antibody titres, neutralising capacity, cross-reactivity.
- d) Areas of specific concern, e.g. respiratory, renal or cardiovascular parameters.
- e) Standard toxicological observations (in-life and post-mortem),

It is worth noting that *in vivo* studies should be designed to detect differences in response and not just the response *per se*. This would apply particularly in specific areas such as immunogenicity.

In vivo toxicology studies should be performed in such a way that the ‘original/reference’ and ‘varied’ products are compared at several dose levels, to allow a comparison of dose-response curves.

The duration of the studies should be sufficiently long to allow detection of any differences in toxicity and/or immunogenicity, and should take into account the intended duration of use.

Ongoing consideration should be given to the use of emerging technologies. (For example: *In vitro* techniques such as ‘real-time’ binding or antigenicity assays may prove useful. *In vivo*, the developing microarray sciences [or “-omics”] may, in the future, present opportunities for comparing minor changes in biological response to pharmacologically active substances by monitoring qualitative and quantitative changes in the profile of biological samples). Interpretation of such studies is an evolving science and the clinical relevance of these techniques remains to be determined. However, useful information may be obtained, particularly since studies would be designed to detect subtle differences in response to two similar products and not just the response *per se*.

3.1.2 Immunogenicity

Immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means (see section 5).

3.1.3 Clinical considerations

In principle, the need for clinical efficacy and safety (other than immunogenicity) data should be approached as if data from confirmatory and comparative efficacy/safety studies were needed. Deviations from this conceptual level should therefore be justified. Important issues that should be taken into account when designing and justifying the clinical program include clinical experience gained with the ‘original/reference’ product if relevant with respect to:

- The stage of development of the product
- The relationship between dose/exposure and efficacy/safety
- Whether a dynamic marker has been accepted as a surrogate marker for clinical efficacy/safety
- The relationship between dose/exposure and this surrogate marker
- Drug/receptor(s) interaction
- Disease-specific mechanisms of action
- Target organ(s) for activity
- Mode of administration
- Pharmacokinetic properties (including biological barriers of relevance)

3.1.3.1 Surrogate markers

Usually in clinical trials, efficacy is defined by a clinical endpoint. Sometimes surrogate markers are used. A dynamic marker is a surrogate marker for efficacy, if therapy-induced changes in that marker to a large extent can explain changes in clinical outcome.

Surrogate markers are usually more sensitive to changes in activity and can be assessed earlier than clinical endpoints and, therefore, may be more useful when comparability has to be shown with clinical data. However, as the goal of the comparative exercise is showing equivalence of the products, usually data are needed concerning the quantitative relationship between the surrogate and the clinical endpoint to enable defining and justifying the equivalence margin in terms of efficacy.

Research in surrogate endpoints is encouraged, though acknowledging that full validation of the surrogate is not an easy process.

There might be situations where the requirements with respect to formal validation are less stringent. Examples include absolute neutrophil count and granulocyte-colony stimulating factor (G-CSF) or early viral load reduction in chronic hepatitis C and alpha interferons. No specific guidance can be given, but face validity and clear linkage between the marker and the disease under consideration are issues of importance. In cases where formal validation of the surrogate marker is missing, a comprehensive justification is expected taking into account the above-mentioned issues and regulatory scientific advice might be advisable.

3.2 Differentiation of requirements

As stated before, the kind of data required will depend on the product and the existing experience.

For a change in the manufacturing process taking place before authorisation the product, the requirements will depend on the stage of development (See also section 2.1.1 of the Guideline on comparability of medicinal products containing biotechnology derived proteins as active substance – quality issues). From a clinical point of view data may be needed when the product intended to be marketed may be different from the one that was used in the pivotal

clinical trials or trials most pertinent to the benefit/risk assessment, whereas in earlier phases comparability might not be an issue. It will be decided on a case-by-case basis, but the differentiation made in this section will be helpful for changes in the manufacturing process before and after marketing authorisation.

A further differentiation may be possible however, based on the level of characterisation of the change. Two situations might be of interest:

- Differences that cannot be characterised in detail or cannot be detected, e.g. due to the complexity of the molecule, but are likely to be present as a consequence of modifications of the production process.
- Differences from the ‘original/reference’ product, found during the comparability exercise, that are well characterised.

3.2.1 Differences that cannot be characterised

If changes are likely to be present, but cannot be characterised, the efficacy and safety of the product need to be confirmed and characterised compared with the ‘original/reference’ product.

Possible differences in efficacy should normally be investigated in studies with the highest probability of showing a difference (see ICH topic E10). The acceptable equivalence margin should be set taking into account clinical relevance and statistical considerations.

If surrogate markers are available, pharmacokinetic (PK)/pharmacodynamic (PD) studies may appropriately fulfil these requirements. Care should be taken in these cases to investigate a reasonable dose range to demonstrate assay sensitivity (see ICH topic E10). The choice of marker(s) should be justified and the margin defining equivalence should be pre-specified and justified.

If no surrogate markers are available and there are no relevant additional non-clinical or clinical data, an equivalence trial, using clinical endpoints will be needed. Assay sensitivity has to be ensured in the design of the trial and the acceptable margin has to be defined and justified.

3.2.2 Differences that are well characterised

Due to the product-specific nature of possible changes in efficacy/safety, it is not possible to present detailed guidance, but, in general, well characterised differences may provide a background for a rational approach with respect to the need for clinical studies. Due to type and/or extent of a change, whether qualitative or quantitative, it may be possible to justify why, for example, only immunogenicity studies are of importance. In other cases where efficacy data are deemed necessary, well conducted and informative receptor interaction studies and a valid pharmacological rationale may support the use of bioequivalence as a surrogate for efficacy.

In case the difference is non-major and there is no change in *in vitro* biological activity, comparable bioavailability data and /or pharmacodynamic studies may be sufficient.

In case the difference is major, e.g. major changes in glycosylation pattern, or difference in *in vitro* / *in vivo* activity, clinical equivalence studies will be necessary, unless otherwise justified.

Generally, in case a change occurs in the primary sequence of the active substance, this will be seen as a major and unacceptable quality problem, that cannot be solved by non-clinical or clinical studies and falls outside the concept of comparability.

3.3 Clinical safety and pharmacovigilance requirements

Possible consequences of a change in the manufacturing process on the safety profile should be discussed and the risk specification should be updated when the variation application is submitted. When appropriate, the Marketing Authorisation Holder (MAH) should include a pharmacovigilance plan within the variation procedure.

The cycle of submission of the periodic safety update reports (PSURs) might be amended (restarted) on a case-by-case basis. If the Variation falls into a normal PSUR cycle within the first five year period, the MAH should give in a separate chapter a cumulative description on reports and any other information that he has received in this context. These reports or information must be evaluated and assessed by the MAH in a scientific manner with regard to causality and, if possible, frequency of events or ADRs.

After a reasonable time period following the manufacturing change and finalisation of the Variation procedure extra requirements from the pharmacovigilance plan may be lifted after consultation with and agreement of the competent authorities.

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

3.4 Timing of the availability of the required non-clinical and/or clinical data

Depending on the situation, data should be available, in the application for authorisation (if relevant), before the variation is approved or after, as a post-authorisation commitment.

Where there are non-clinical data relevant for the impact of the change on efficacy and/or safety of the product, these should be submitted before approval.

In principle, clinical data, if required, need to be available before approval. Depending on the product and the indication, approval might be based on pharmacodynamic data, provided that the clinical endpoint results will be provided after approval.

For immunological data see section 5.2 Changes to the active substance and to the formulation.

4. MEDICINAL PRODUCT SIMILAR TO ANOTHER ONE ALREADY AUTHORISED IN THE EU

In any cases, the company should justify, in the dossier, its approach chosen during the development of the product and might want to contact the EMEA before starting the development.

When an application for a biological medicinal product containing a biotechnology-derived medicinal protein as active substance, which refers to an original/reference medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of the data protection period, in accordance with the provisions laid down in part II, section 4 of Annex I to Directive 2001/83/EC, as amended, the following approach shall be applied:

The company pursues to demonstrate that medicinal product is similar in terms of quality, safety and efficacy to a medicinal product already authorised in the EU. It may not be necessary to repeat all safety and efficacy studies if the applicant can demonstrate that 1) it is possible to characterise the product in detail with respect to physico-chemical properties and *in vitro* activity, and 2) comparability can be shown from a chemical-pharmaceutical perspective. During the whole comparability exercise, the same 'reference' product should be used for all three parts of the dossier.

In case the ‘reference’ product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. Justification will depend on e.g., clinical experience, available literature data for the ‘reference’, whether or not the same receptor(s) are involved in all indications, pre-clinical data and immunogenicity.

Safety data will be needed prior to marketing authorisation, but also post-marketing (see section 4.2.4 Safety) as possible differences might become evident later, even though comparability with regard to efficacy has been shown.

4.1 Non-clinical data

The company should take into consideration the “Note for Guidance on Pre-clinical Safety Evaluation of Biotechnology Derived Pharmaceuticals (CPMP/ICH/302/95)”. All the points raised in this document will need to be addressed in the dossier. Where a comparability exercise is conducted, the same considerations as in section 3.1.1 of this document apply. If there are other, case-specific safety concerns (e.g. relating to new excipients or local tolerance) these might be resolved by performing appropriate standard non-clinical studies prior to administration of the new product to man in clinical trials. The approach taken will need to be fully justified in the non-clinical overview.

4.2. Immunogenicity

Immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means. If in comparison with the reference product, differences in the quantity or type of antibody are found, this has to be further investigated (see section 5 Immunogenicity).

4.3. Clinical data

The requirements depend on the type of product and the therapeutic areas. Available guidelines should be followed.

Generally, demonstration of equivalence concerning bioavailability and pharmacodynamic action(s) using equivalent dosing will be required. As mentioned before, ‘equivalence’ has to be defined a priori and the choice of the pharmacodynamic parameter(s) justified.

In addition, clinical trials demonstrating equal efficacy (“equivalence trials”, see ICH topic E9, CPMP/EWP/482/99) will generally be necessary between the product to be assessed and the chosen ‘reference’. The kind of trials, the duration and type of endpoint (e.g., clinical or surrogate, see sections 3.1.3 Clinical considerations and 3.1.3.1 Surrogate markers) depend on experience, type of product, therapeutic area and the availability of accepted surrogate endpoints.

As for all equivalence designs, assay sensitivity (see ICH topic E10) has to be ensured. If this cannot be done or is shown to be not feasible, other designs should be explored and the consequences discussed with the competent authorities.

4.4. Safety

Even if the efficacy is shown to be comparable, the product may exhibit a different safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Data from pre-authorisation clinical studies may be too small to identify these differences. Therefore, safety of these products must be monitored closely on an ongoing basis during the post-marketing phase including a risk-to-benefit assessment.

The MAH 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. Provision of reasonable plausibility for such possibly different tolerability should be given.

Within the authorisation procedure the MAH should present a pharmacovigilance plan in accordance with current EU legislation and Pharmacovigilance guidelines.

In the PSURs submitted within the first five year period, the MAH should address reports and any other information on tolerability that he has received. These reports or information must be evaluated and assessed by the MAH in a scientific manner with regard to causality and, if possible, frequency of events or ADRs.

In addition, the compliance of the marketing authorisation holders with commitments (where appropriate) and their pharmacovigilance obligations will be closely monitored.

Therefore, pharmacovigilance systems (as defined in the current EU legislation) and procedures (as described in the current EU guidelines) to achieve this monitoring should be in place when a marketing authorisation is granted.

5. IMMUNOGENICITY

5.1 Prediction of immunogenicity

The factors triggering immune reactions against biotechnology-derived proteins are often not fully understood in individual cases. In general, however, the occurrence of immunogenicity is influenced by the properties of the active substance and finished product. Changes to the manufacturing process may lead to changes that can trigger an immune response as discussed under 5.2. Furthermore, host factors including genotype and concomitant diseases associated with immune dysregulation, previous exposure to other therapeutic proteins that might cause cross reactivity, could also play a part. The route of administration can modify the host immune reaction. Repeated administration of an antigen may increase the likelihood of an immune response as compared to one-off treatment.

In assessing possible risk factors for immunogenicity, previous experience with the product or other products of the same class, should also be taken into account, in addition to the factors discussed above.

5.2 Changes to the active substance and to the finished product²

A change in the manufacturing process may result in changes in protein folding or in glycosylation. These changes may not always be detected by physicochemical methods, but may still cause a change in immunogenicity. Post-translational differences may occur between various expression systems although the genes themselves are identical. Furthermore, the chemical process used for extraction and purification of the therapeutic protein may result in changes that can enhance immunogenicity. Product and process-related impurities may affect immunogenicity. Some changes, such as aggregation, may be observed after modification of the formulation and/or change in the storage conditions and may induce immune responses. Furthermore, a change in excipients may have an effect on the immunogenicity of the active substance.

5.3 Investigation of immunogenicity

Virtually all biotechnology-derived therapeutic proteins elicit some level of antibody response. Those antibodies associated with clinical consequences require closer monitoring.

² See “Note for guidance on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/BWP/3207/00)” for more detailed discussion on the quality aspects.

The assessment of immunogenicity requires validated antibody assays, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies, pharmacokinetics/pharmacodynamics and efficacy and safety. Especially, the role of immunogenicity in events related to hypersensitivity, infusion reactions, autoimmunity and loss of efficacy should be considered. In addition, post-marketing program may be required as discussed below.

The Applicant should present a rationale for the proposed antibody-testing strategy. The screening assays should be sensitive enough to detect low titre antibodies as well as antibodies to conformational and linear epitopes. An assay for neutralising antibodies should be available for further characterisation of antibodies detected by the screening assays. These assays should be validated. Standard methods and international standards should be used whenever possible. In the planning of studies of immunogenicity, the predisposing factors for immunogenicity discussed above and the experience gained from existing products should be considered. The duration of studies must be sufficiently long; the periodicity and timing of sampling for testing of antibodies should be justified. The value of antibody testing in the monitoring of the individual patient should be critically evaluated and recommended as a routine measure only if it can affect therapeutic decision-making.

5.4 When to study immunogenicity?

The issue of immunogenicity must always be considered when a claim of comparability is made, especially when repeated administration is proposed. The need for testing after changes have been made to the manufacturing process of an existing product should be assessed on a case-by-case basis. Immunological studies are expected if physico-chemical characterisation is not sufficient due to the complexity of the molecule and an impact on immunogenicity cannot be excluded with reasonable certainty.

In principle, pre-authorisation studies are required for a claim of comparability to another product. Pre-authorisation studies may be required for changes having a potential or a documented impact on the quality profile. In view of the unpredictability of the onset and incidence of immunogenicity, post-marketing monitoring of antibodies at predetermined intervals will be required for at least one year for a new biotechnological product and may be required after a change to an existing product. A pharmacovigilance plan and a pharmacovigilance specification for post-marketing monitoring should be included in the marketing authorisation application (see section 4.1.4). If the risk of serious but rare immune mediated response is considered to be high, either because of signals detected before the authorisation or previous experience with similar products, a special risk management programme may be required. Special consideration should be given to those products where there is a risk that the immune response could affect the endogenous protein that has unique biological functions.