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DRAFT

GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS

NON-CLINICAL AND CLINICAL ISSUES

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This guideline replaces guideline the guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/3097/02)

Comments should be provided electronically in word format using this template to: BMWP.secretariat@emea.europa.eu

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Manufacturers of biotechnological/biological products frequently make changes to manufacturing processes of their products both the pre- and post-approval. This guideline gives advice on the non-clinical and clinical requirements of the comparability exercise comparing post-change product to pre-change product.

Demonstration of comparability is a sequential process, beginning with quality studies (limited or comprehensive) and supported, as necessary, by non-clinical and/or clinical studies.

This guideline will address the requirements for non-clinical and/or clinical bridging studies to demonstrate that the modification has no impact on safety and efficacy.

The selection of non-clinical versus clinical testing is product-driven, i.e. a model should be chosen that best detect clinically relevant differences with sufficient accuracy

1. INTRODUCTION

Marketing authorisation holders frequently introduce changes in the manufacturing process of a given product (both before and after the granting of a marketing authorisation). The marketing authorisation holder will have to demonstrate or justify that both versions of the product have comparable quality, safety and efficacy. 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.

For most changes to the manufacturing process, physico-chemical and *in vitro / in vivo* biological testing can demonstrate that there is no difference in quality of the product that could adversely impact the safety and efficacy of a product. Thus the comparability exercise may be limited to strict process validation of the change or be extended to various quality criteria such as in-process controls, thorough analytical and biological characterisation of the product and stability data. However, sometimes an effect on efficacy and/or safety can be expected on the basis of observed difference(s)or cannot be ruled out in spite of the state of the art physico-chemical and biological tests. In such cases, additional non-clinical and clinical studies will be necessary. The type and extent of such studies are variable and will be dependent on numerous factors related to the drug substance and the drug product such as the stage of development for products not yet authorised, the findings in the physico-chemical and biological comparability exercise as well as the intended clinical use.

2. SCOPE

The principles adopted and explained in this document apply to:

- Proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. These proteins and polypeptides are produced by recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures;
- Products where manufacturing process changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of pre-change and post-change product;
- Products where manufacturing process changes are made in development or for which a marketing authorisation has been granted.

The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. In this case, manufacturers are advised to consult relevant guidelines and the competent Regulatory Authority to determine applicability.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and part II of the Annex I to Directive 2001/83 as amended.

4. MAIN GUIDELINE TEXT

4.1 Need for (non)clinical studies – a risk-based approach

Demonstration of comparability is a sequential process. Thus, the extent of the comparability exercise will vary. If a manufacturer can provide evidence of comparability through physico-chemical and biological studies, non-clinical or clinical studies with the post-change product are not warranted. In other cases, additional (non)clinical data will be required.

The need, extent and nature of non-clinical and clinical comparability studies will be determined on a case-by-case basis in consideration of various factors that may be associated with a risk, such as:

- The nature, and extent of differences demonstrated by the physico-chemical and biological *in vitro* characterisation, including product-related substances, impurity profile, stability and excipients. Thus, well-characterised differences may provide a background for a rational and focused approach with respect to the need for (non)clinical studies.
- Product complexity, including heterogeneity and higher order structure and the availability, capabilities and limitations of analytical tests. If the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product, additional non-clinical and/or clinical testing may be necessary.
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy
- Relationship between the therapeutic protein and endogenous proteins and the severity of (potential) consequences for immunogenicity; e.g. risk of autoimmunity
- Mode(s) of action: unknown or multiple modes of action complicate the evaluation of the impact of changes
- Therapeutic indications/target patient groups - The impact of possible differences can vary between the target populations covered by the different indications.
- Posology, e.g., dosing regimen and route of administration, for instance, repeated administration via subcutaneous route is more likely to be associated immunogenicity than intravenous administration of a single dose.
- The therapeutic window/dose-response curve
- Previous experience, e.g., immunogenicity, safety. Experience with the original product or with other products in the same class can be relevant.

For products in development, all these points above should be taken into consideration. However, the extent of the comparability studies will likely increase if manufacturing changes are introduced at the later stages of clinical development. A change after conduct of pivotal efficacy and safety studies represents the most challenging situation.

The selection of non-clinical versus clinical testing is product-driven, i.e. a model should be chosen that best detect clinically relevant differences with sufficient accuracy.

4.2 Non-clinical data

If evidence from physico-chemical studies and quality-related biological studies alone is not sufficient to establish comparability of the “varied” and the “original” product, data from non-clinical studies can provide useful signals of potential therapeutic differences.

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 the design of an

appropriate non-clinical study program requires a clear understanding of the product characteristics. 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.

Non-clinical studies should be comparative in nature and should be designed to detect differences in response between the "varied" and the "original" product and not just the response *per se*. Sufficient information and cross-referencing to other sections should be provided in the non-clinical section to justify the approach taken in subsequent studies.

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 justified in the non-clinical overview.

- *In vitro* studies

Assays like 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 alterations in reactivity have occurred and to determine the likely causative factor(s) if comparability cannot be established.

- *In vivo* studies

If there are specific uncertainties or concerns regarding safety, *in vivo* studies in one or more suitable animal model may be considered. Greater reliance would be placed on results from studies in a species shown for the 'original' product to be a relevant model for man. The final formulation should preferably be used. State of the art methods should be employed.

In general and where the model allows, consideration should be given to monitoring a number of endpoints such as:

- Changes in pharmacodynamic parameters relevant to the clinical application, e.g. duration of action.
- Changes in pharmacokinetic parameters, e.g. clearance
- Specifically designed toxicological observations (in-life and post-mortem). This design should be justified, taking into consideration the intended duration of clinical use.
- The immune response, e.g. antibody titres, neutralising capacity, cross-reactivity. Although the predictive value of animal models for immunogenicity in humans is low, immunogenicity endpoints should be included in repeated dose toxicty studies to aid in the interpretation of these studies.

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.

4.3 Clinical studies

Requirement for a dedicated clinical comparative efficacy and safety study is dependent on the stage of development. Companies frequently introduce changes during the development of a given product prior to marketing authorisation application. If a manufacturing change is introduced before the confirmatory trial(s), the additional data required for the comparability exercise might be fewer than those needed for changes introduced after the confirmatory trial(s) or after approval.

- *Changes in the manufacturing process before initiation of confirmatory trials*

For this situation, adequate data from physico-chemical, biological, and sometimes also non-clinical or clinical comparability studies such as a single dose pharmacokinetic study, are generally sufficient in order to demonstrate that the non-clinical and clinical data obtained before the change has been introduced are still valid and can be extrapolated to the post-change product.

- *Changes in the manufacturing process after confirmatory trials or after approval*

If a manufacturing change takes place after the confirmatory trial(s) has been performed, or after approval, a more thorough comparability exercise is required, including physicochemical and biological in vitro studies, and pharmacokinetic and / or pharmacodynamic comparability studies. If this comparability exercise cannot rule out an impact on the efficacy and safety profile of the drug, additional clinical study (ies) may have to be performed. Deviations from this conceptual level should be justified

- *Further criteria influencing the requirement of comparative clinical data*

Further important issues that should be taken into account when designing and justifying the clinical program include results of any non-clinical studies and any clinical experience gained with the "original" product, if relevant, with respect to:

- 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 studies

Pharmacokinetic studies are an essential part of the comparability exercise. Since the aim is to demonstrate comparability and not the characterization of clinical pharmacology of the product *per se*, such studies should be comparative.

A single-dose crossover study is, in principle, acceptable due to usually lower variability than in head-to-head comparisons. However, factors like immunogenicity and possible related alterations of pharmacokinetics and/or pharmacodynamics should be considered

The route of administration should be in accordance with the intended clinical use. If the product can be administered by more than one route (e.g. s.c. and i.v.), it may become necessary to test all routes. The selected dose should be in the steep part of the dose-response curve. The choice of the population (healthy volunteers versus patients) is primarily driven by the mode of action of the product. Since PK and PD studies are preferably combined, the choice of the population should consider the PD effects to be shown, i.e. if they are detectable in a relevant manner in the population of choice. The possibility of a carry-over effect should be considered when designing such study.

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

Pharmacodynamic studies

Pharmacodynamics should preferably be evaluated as part of the comparative pharmacokinetic study, since alterations in pharmacodynamics can sometimes be explained by altered kinetics. Again, studies should be comparative in nature and not merely show the pharmacodynamics of the product *per se*.

- *Markers for primary and secondary pharmacodynamics*

As a principle, an endpoint should be selected that fulfils the following requirements: (1) sensitive enough to detect small differences, (2) measurable with sufficient precision, (3) clinically relevant for the target population. Care should be taken in these cases to investigate a reasonable dose range to demonstrate assay sensitivity. Studies at more than one dose level may be useful (see ICH topic E10).

The choice of marker(s) should be justified and the margin defining equivalence should be pre-specified and justified.

In this respect, the choice of the population should be justified. Demonstration of certain primary or secondary PD markers might only be apparent in the diseased population as opposed to healthy volunteers. For example, immunomodulators aiming at modulating pathologically altered immune effector cells would not necessarily exert similar effects in healthy volunteers.

- *PD markers as substitutes for efficacy*

Usually in clinical trials, efficacy is defined by one or more clinical endpoint(s). Sometimes PD markers are used. A pharmacodynamic marker is a relevant marker for efficacy, if therapy-induced changes in that marker to a large extent can explain changes in clinical outcome.

PD markers are usually more sensitive to changes in activity of the product and can be assessed earlier than clinical endpoints and, therefore, they might in some cases represent the most appropriate endpoint. However, as the goal of the comparative exercise is showing equivalence of the products, usually data are needed concerning the quantitative relationship between the PD marker and the clinical endpoint to enable defining and justifying the equivalence margin in terms of efficacy. Sometimes it may be useful to use more than one PD marker.

Research in surrogate endpoints by the applicants / marketing authorisation holders is encouraged, since a surrogate marker will be useful in the course of product development.

Efficacy studies

- *Study design*

If no suitable markers exist, or if pharmacodynamic studies fail to establish comparability clearly, a comparative equivalence clinical trial using clinical endpoints will be required. Again, studies should be comparative in nature, comparing the post-change product with the pre-change product. Equivalent therapeutic efficacy should be demonstrated. Usually, clinical studies should be double-blind to avoid bias. 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, and be pre-specified.

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

- *Selection of the most relevant patient population/therapeutic indication*

Since therapeutic proteins can be used for different indications and/or different patient populations, differential impact on efficacy and/or safety needs to be considered. Usually, a patient population or indication should be chosen where differences are best distinguishable, i.e. the most sensitive model. The choice, however, will also depend on the susceptibility and vulnerability of this population to potential safety problems, and will have to be justified by the applicant. The Applicant needs to thoroughly discuss and justify if efficacy and safety results of the comparative study in one indication or population can reasonably be assumed to be applicable to other populations or indications.

- *Selection of appropriate endpoints*

As a principle, endpoints should be selected that show differences with the highest accuracy. The clinical requirements for comparative studies being part of a comparability exercise can be different from those for conventional confirmatory studies. For marketed products, the endpoints might not necessarily be those, which had been selected for the pivotal confirmatory trials if they are not sufficiently suitable for detection of differences. As noted above, pharmacodynamic or other markers like imaging techniques can be more suitable than genuine clinical endpoints. The choice of endpoints needs to be fully justified.

- *Study duration*

The study duration is essentially driven by the choice of the clinical endpoint. The duration should be sufficient to detect also minor differences with sufficient accuracy. Available data from literature should be included in the justification and discussion of study duration. Since safety data evaluation is an essential part of the clinical comparability exercise, the study duration should also be determined with the aim of detecting relevant differences of safety findings adequately.

- *Study size*

The calculation of the number of cases required should not solely be based on considerations on clinical efficacy, but also on detection of differences in safety (see below).

Clinical safety and pharmacovigilance requirements

Even if the efficacy is shown to be comparable, the post-change product may exhibit a difference in the 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 adverse effect profiles of the pre and post changed product. Care should be given to compare the type, severity and frequency of the adverse reactions between the pre- and post-change product.

Applicants should in their discussion of adverse events not only include the incidence, but also discuss possible differences in clinical presentation (duration, magnitude, reversibility, response to treatment etc.).

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 the changes in the manufacturing process.

- *Extent of the safety database*

In general, safety data can be gathered as part of the clinical study aiming at establishing equivalent efficacy. Study duration and sample size calculation should consider both frequency and magnitude of reasonably expectable adverse events as well as the clinical setting of the use of the drug (intended for acute / chronic use etc.) (see also ICH guideline ICH E1). Again the general rule applies that the aim of such trial is not the detection of adverse events *per se*, but the evaluation of differences in occurrence.

- *Safety endpoints*

Specific safety endpoints should be selected, taking into account both the typical safety findings known for this product and/or this product class and potential other safety findings, which can be deduced from the mechanism of action. Since unprecedented safety findings might occur, applicants are discouraged from setting up methods in the study protocols solely aiming at the detection of known safety issues. The evaluation of comparative immunogenicity should be integral part of safety evaluation (see Guideline on Immunogenicity of therapeutic proteins).

Risk Management Program

Within the authorisation procedure the applicant should present an updated of the risk management plan in accordance with current EU legislation and pharmacovigilance guidelines. This should take into account risks identified during product development and potential risks.

Any specific safety monitoring imposed to the pre-change product and/or product class should be taken into consideration in the risk management plan, in accordance with EU legislation and guidelines on RMP.(update the list of guidelines to include the mentioned here)..

In the PSURs submitted according current EU legislation, the marketing authorisation holder should address reports and any other information on tolerability that might be related to a process change. The cycle of submission of the periodic safety update reports (PSURs) might be amended (restarted) on a case-by-case basis.

Timing of the comparability data

Non-clinical data relevant for the impact of the change on efficacy and/or safety of the product should be submitted before approval.

In principle, clinical data, if required, need to be available before implementation of the change in the manufacturing process, i.e. marketing the new version of the product. Depending on the product and the indication, approval of the process change might be based on pharmacodynamic data. Additional clinical/safety data, including immunogenicity data, may be provided after approval.

REFERENCES

- ICH topic Q5E, Step 4 Note for Guidance on Biotechnological/Biological Products Subject to changes in their Manufacturing Process (CPMP/ICH/5721/03 final approval by CHMP December 2004)
- Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/3097/02)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/05)
- Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99)
- ICH topic S6 - Note for guidance on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)
- Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)
- Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00
- 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)
- ICH topic E 1 Population exposure: The extent of population exposure to assess clinical safety (CPMP/ICH/375/95)