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Pre-authorisation Evaluation of Medicines for Human Use

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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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EXECUTIVE SUMMARY

The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/42832/05/) lays down the non-clinical and clinical requirements for a biological medicinal product claiming to be similar to another one already marketed.

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies as well as the risk management plan with special emphasis on studying the immunogenicity of the similar biological medicinal product.

1. INTRODUCTION

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 a reference medicinal 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 appropriate comparability exercise `will be required to demonstrate that the similar biological and reference medicinal 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/49348/05).

The Marketing Authorisation (MA) application dossier of a biological medicinal product claimed to be similar to a reference medicinal product already authorised shall provide a full quality dossier. Comparable clinical efficacy and safety has to be demonstrated. The principles for this exercise are laid down in this guideline. Product class specific annexes will supplement this guideline 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 medicinal product should be used for all three parts of the dossier (i.e. quality. safety and efficacy aspects).

In case the originally authorised medicinal 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. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed. 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 (see section 7), and in conjunction with Part II of the Annex I of Directive 2001/83/EC, as amended.

3. LEGAL BASIS

Directive 2001/83/EC, as amended and Part II of the Annex I of Directive 2001/83/EC, as amended.

4. MAIN GUIDELINE TEXT

4.1 NON-CLINICAL DATA

Before initiating 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 medicinal 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:

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 establish comparability in reactivity and the likely causative factor(s) if comparability cannot be established.

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 medicinal product.
- 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.

Normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for similar biological medicinal products, unless indicated of results of repeat dose studies.

4.2 CLINICAL STUDIES

The requirements depend on the existing knowledge about the reference biological medicinal product and the claimed therapeutic indication(s). Available product / 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 the test product as produced with the final manufacturing process and therefore representing the quality profile of the batches to become commercialised. Any deviation from this recommendation should be justified and supported by adequate additional data.

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for demonstrating clinical comparability.

Pharmacokinetic studies

Comparative PK studies designed to demonstrate clinical comparability between the similar biological medicinal product and the reference medicinal 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 "clinical comparability" 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 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 clinical comparability 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 clinical comparability studies, initially developed for chemically derived, orally administered products may not be appropriate and the clinical comparability limits should be defined and justified prior to conducting the study.

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 medicinal 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.

Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

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

- The PK of the reference medicinal product are well characterised.

- There is sufficient knowledge of the pharmacodynamic properties of the reference medicinal 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 medicinal product (the therapeutic "concentration-response" curve) is sufficiently characterised.
- At least one PD marker is accepted 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 comparability of the biological medicinal products, care should be taken to investigate a relevant dose range to demonstrate assay sensitivity (see ICH topic E10).

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

Efficacy trials

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

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

4.3 CLINICAL SAFETY AND PHARMACOVIGILANCE REQUIREMENTS

Even if the efficacy is shown to be comparable, the similar biological medicinal 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 test and the reference medicinal product. Care should be given to compare the type, severity and frequency of the adverse reactions between the similar biological and the reference biological medicinal products.

Data from pre-authorisation clinical studies normally are insufficient to identify all potential 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.

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

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. Any specific safety monitoring imposed to the reference medicinal product or product class should be taken into consideration in the risk management plan.

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

In the PSURs submitted according current EU legislation, the marketing authorisation holder should address reports and any other information on tolerability that the company 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.

4.4 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

The consequences of immunogenicity may vary considerably, ranging from. irrelevant for therapy, to serious and life-threatening. Therefore, the immunogenicity issue has become a subject of concern in the development and approval of biopharmaceuticals. An immune response to the product may 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 pharmacokinetic, pharmacological and safety 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 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.

The applicant should consider the possibility of antibodies to process related impurities

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 seriously affect the endogenous protein and its unique biological function. Antibody testing should be considered as part of all clinical trials protocols. 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 encourage the reporting of relevant adverse events, including events related to loss of efficacy.

REFERENCES

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMEA/CHMP/4924/05)
- Guideline on similar biological products (CHMP/437/04), the so-called 'overarching guideline'
- ICH topic S6 - Note for guidance on Preclinical 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 preparation)
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP 96286/2005)
- Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03 - Final approval by CHMP on PHV