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Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

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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* (EMA/CHMP/BMWP/42832/05 Rev.1) lays down the non-clinical and clinical requirements for a similar biological medicinal product (“biosimilar”).

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, and efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies, including immunogenicity, as well as the risk management plan.

The current revision covers the following topics: a stepwise approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan, and pharmacovigilance, and extrapolation of safety and efficacy. The guideline recommends a stepwise conduct of non-clinical and clinical studies.

1. Introduction

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

The Marketing Authorisation (MA) application dossier of a biosimilar medicinal product shall provide a full quality dossier together with data demonstrating comparability with the reference medicinal product by using appropriate physico-chemical and *in vitro* biological tests, non-clinical studies and clinical studies.

The quality issues relevant for demonstration of biosimilar comparability are addressed in the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues* (EMA/CHMP/BWP/247713/2012).

The principles for the non-clinical and clinical parts of the biosimilar comparability exercise are laid down in this guideline. Product class specific guidelines will supplement this guideline where a need is identified.

The nature and complexity of the reference product have an impact on the extent of the (non)clinical studies to confirm biosimilarity. The differences observed in the physico-chemical and biological analyses will guide the planning of the (non-)clinical studies. Other factors that need to be taken into consideration are the mode of action of the active substance (e.g. receptor(s) involved) in all the authorised indications of the reference product and pathogenic mechanisms involved in the disorders included in the therapeutic indications (e.g. mechanisms shared by various therapeutic indications) as well as the immunogenicity of the reference medicinal product.

The applicant should review data from the reference product on the predictive value of *in vitro* assays/animal models as well as correlations between dose/exposure and pharmacodynamics. In addition, the applicant should look at the correlation between pharmacodynamics and clinical response. The availability of suitable biomarkers may abbreviate the (non-)clinical development. The safety profile of the reference product will mainly determine the focus of the clinical safety studies both pre- and post-authorisation.

If the biosimilar comparability exercise indicates that there are relevant differences between the biosimilar and the reference medicinal product, making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application, should be considered instead (see “Guideline on similar biological products” (CHMP/437/04 Rev. 1)).

2. Scope

This guideline addresses the general principles for the non-clinical and clinical development and assessment of the marketing authorisation applications of biosimilars containing biotechnology-derived proteins as active substance(s). Nevertheless, the principles explained in this document could apply to other biological products, on a case by case basis. 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).

3. Legal basis and relevant guidelines

- Directive 2001/83/EC, as amended in particular Directive 2001/83/EC Art 10(4) and Part II of the Annex I of Directive 2001/83/EC, as amended.
- Directive 2010/63/EU on the protection of animals used for scientific purposes.

For the relevant CHMP/ICH guidelines, please see the website of the European medicines Agency (<http://www.ema.europa.eu>): Human medicines > Scientific guidelines > Multidisciplinary > Biosimilar. In particular, the following guidelines should be read in conjunction:

- Guideline on similar biological products (CHMP/437/04 Rev. 1), the so-called ‘overarching guideline’
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMA/CHMP/BWP/247713/2012)
- Q5E Comparability of biotechnological/biological products (CPMP/ICH/5721/03)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99)
- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMA/CHMP/BMWP/14327/2006)
- Guideline on Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)
- Guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009)
- Product class-specific guidelines on various biosimilar products

- Guidelines on good pharmacovigilance practices (please see the website of the European medicines Agency (<http://www.ema.europa.eu>) – Human regulatory – Pharmacovigilance – Good Pharmacovigilance Practices)

4. Non-clinical studies

To support biosimilarity, relevant non-clinical studies should be performed before initiating clinical trials. A stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product. Analytical studies (see Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues) and *in vitro* pharmacotoxicological studies should be conducted first and a decision then made as to the extent of what, if any, *in vivo* work in animal studies will be required.

It is important to note that, to design an appropriate non-clinical study programme, a clear understanding of the reference product characteristics is required. Results from the physico-chemical and biological characterisation studies (i.e. comparability of the biosimilar to the reference product) should be reviewed from the point-of-view of potential impact on efficacy and safety.

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

4.1. Step 1: *In vitro* studies

In order to assess any potential difference in biological activity between the biosimilar and the reference medicinal product, data from a number of comparative *in vitro* studies, some of which may already be available from quality-related assays, should normally be provided.

These studies should include relevant assays on:

- *Binding* to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmacotoxicological effects and/or pharmacokinetics of the reference product.
- *Signal transduction and functional activity/viability* of cells known to be of relevance for the pharmacotoxicological effects of the reference product.

The studies should be comparative in nature and should not just assess the response *per se*. To obtain unambiguous results, the methods used should be scientifically valid and suitable for their purpose.

The studies should be sensitive, specific and sufficiently discriminatory to provide evidence that observed differences in quality attributes are clinically not relevant. The studies should compare the concentration–activity/binding relationship of the biosimilar and the reference medicinal product at the pharmacological target(s), covering a concentration range where potential differences are most sensitively detected.

They should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of the material intended for clinical use. Assay and batch-to-batch variability will affect the number needed. The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the biosimilar and the reference product and on the similarity of both products.

Together, these assays should cover the whole spectrum of pharmacological/toxicological aspects known to be of clinical relevance for the reference product and for the product class.

The applicant should discuss to what degree the *in vitro* assays used are representative/predictive for the clinical situation according to current scientific knowledge.

Since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, these assays can be considered as paramount for the non-clinical biosimilar comparability exercise.

4.2. Step 2: Determination of the need for *in vivo* studies

It is acknowledged that biotechnology-derived proteins may mediate *in vivo* effects that cannot be fully elucidated by *in vitro* studies. Therefore, non-clinical evaluation in *in vivo* studies may be necessary to provide complementary information, provided that a relevant *in vivo* model with regard to species or design is available.

Factors to be considered when the need for *in vivo* non-clinical studies is evaluated, include, but are not restricted to:

- Presence of potentially relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).
- Presence of potentially relevant quantitative differences in quality attributes between the biosimilar and the reference product.
- Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins.

Although each of the factors mentioned above do not necessarily warrant *in vivo* testing, these issues should be considered together to assess the level of concern and whether there is a need for *in vivo* testing.

If the biosimilar comparability exercise for the physicochemical and biological characteristics and the non-clinical *in vitro* studies (see step 1) are considered satisfactory and no issues are identified in step 2 which would block direct entrance into humans, an *in vivo* animal study is usually not considered necessary.

If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot sufficiently be characterised on a quality and *in vitro* level, *in vivo* studies may be necessary. The Applicant should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers.

If there is a need for additional *in vivo* information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered.

If a relevant *in vivo* animal model is not available, the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk.

4.3. Step 3: *In vivo* studies

If an *in vivo* evaluation is deemed necessary, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information. Animal studies should be designed to maximise the information obtained. The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any *in vivo* study. Depending on the endpoints used, it may not be necessary to sacrifice the animals at the end of the study. The duration of the study (including observation period) should be justified, taking into consideration the PK behaviour of the reference medicinal product and its clinical use.

When the model allows and if not otherwise justified, the PK and PD of the biosimilar and the reference medicinal product should be quantitatively compared, including, if feasible, a dose concentration-response assessment including the intended exposure in humans.

For safety studies a flexible approach should be considered, in particular if non-human primates are the only relevant species. The conduct of standard repeated dose toxicity studies in non-human primates is usually not recommended. If appropriately justified, a repeated dose toxicity study with refined design (e.g. using just one dose level of biosimilar and reference product and/or just one gender and/or no recovery animals) or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions) may be considered. For repeated dose toxicity studies where only one dose is evaluated, this would usually be selected at the high end of the dosing range and should be justified on the basis of expected toxicity of the reference medicinal product.

The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended. Due to the different production processes used by the biosimilar and reference product manufacturers, qualitative differences of process related impurities can occur (e.g. host cell proteins). The level of such impurities should be kept to a minimum, which is the best strategy to minimise any associated risk.

Qualitative or quantitative difference(s) of product-related variants (e.g. glycosylation patterns, charge variants) may affect biological functions of the biotechnology-derived protein and are expected to be evaluated by appropriate *in vitro* assays. These differences and impurities may have an effect on immunogenic potential and the potential to cause hypersensitivity. It is acknowledged that these effects are difficult to predict from animal studies and should be further assessed in clinical studies.

Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of *in vivo* studies in animals. Therefore, blood samples should be taken and stored for future evaluations of pharmacokinetic/toxicokinetic data if then needed.

Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars.

Studies on local tolerance are usually not required. However, if excipients are introduced for which there is no or little experience with the intended clinical route of administration, local tolerance may need to be evaluated. If other *in vivo* studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies.

5. Clinical studies

It is acknowledged that the manufacturing process of the biosimilar product will be optimised during development. However, it is recommended to generate the clinical data required for the biosimilar comparability exercise with the biosimilar product derived from the commercial 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 bridging data (as described in guideline ICH Q5E).

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

5.1. Pharmacokinetic studies

Comparative pharmacokinetic (PK) studies designed to demonstrate similar PK profile of the biosimilar and the reference medicinal product with regard to key PK parameters are an essential part of the biosimilar development programme.

The design of a PK study depends on various factors, including clinical context, safety, PK characteristics of the reference product (target-mediated disposition, linear or non-linear PK, time-dependency, half-life, etc.) as outlined in the *Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins* (CHMP/EWP/89249/2004) and, as applicable, the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Furthermore, bioanalytical assays should be appropriate for their intended use and adequately validated as outlined in the *Guideline on bioanalytical method validation* (EMA/CHMP/EWP/192217/2009).

The biosimilar comparability limits for the main PK parameters should be defined and justified prior to conducting the study. The criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, orally administered products, may be a reasonable basis for planning comparative pharmacokinetic trials for biologicals in the absence of specific criteria. However, the interpretation of bioequivalence studies for biologicals is less straightforward than for small molecules. In the latter case the molecules are considered identical, whilst for biologicals, PK is used to detect possible differences in the interaction with the body between the originator and the biosimilar. This means that observing 90% CIs of ratios of biosimilar to reference product within a pre-specified, justified acceptance range may not, by itself, be sufficient. The location and the width of the confidence interval should also be taken into account in the interpretation of similarity. For example, statistically significant differences in 90% CIs within the justified acceptance range regarding relevant PK parameters would need to be explained and justified as not to preclude biosimilarity. On the other hand, if the 90% CI crosses the prespecified boundaries the applicant would need to explain such difference and explore root causes. Correction for protein content may be acceptable on a case-by-case basis if pre-specified and adequately justified, with the results from the assay of the test and reference products being included in the protocol.

Although the comparison of target-mediated clearance is of major importance in the biosimilarity exercise, it may not be feasible in patients due to major variability in target expression, including variability over time. However, since *in vitro* studies are expected to show comparable interaction between the biosimilar and its target(s) (including FcRn for a mAb), the absence of a pivotal PK study in the target population is acceptable, if additional PK data are collected during the efficacy, safety and/or PD studies as this allows further investigation of the clinical impact of variable pharmacokinetics and possible changes in the PK over time. This can be achieved by determining the PK profile in a subset of patients or by population pharmacokinetics.

A single dose cross-over study with full characterisation of the PK profile, including the late elimination phase, is preferable. A parallel group design may be necessary with substances with a long half-life and/or a high risk of immunogenicity. The doses in the single dose PK biosimilar comparability study in healthy volunteers may be lower than the recommended therapeutic doses. PK studies are not always feasible in healthy volunteers. In this case, the PK needs to be studied in patients as part of a multiple dose study, if a single dose study is not feasible. A sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.

If the reference product can be administered both intravenously and subcutaneously, the evaluation of subcutaneous administration will usually be sufficient as it covers both absorption and elimination. Thus, it is possible to waive the evaluation of intravenous administration if biosimilar comparability in both absorption and elimination has been demonstrated for the subcutaneous route. Omission of the

PK study of intravenous administration needs to be justified, e.g., in cases when the molecule has an absorption constant which is much slower than the elimination constant (flip flop kinetics).

In a single dose PK study, the primary parameters are the $AUC_{(0-\infty)}$ for intravenous administration and $AUC_{(0-t)}$ and usually C_{max} for subcutaneous administration. Secondary parameters such as t_{max} , volume of distribution, and half-life, should also be estimated. In a multiple dose study, the primary parameters should be the truncated AUC after the first administration until the second administration (AUC_{0-t}) and AUC over a dosage interval at steady state (AUC_{τ}). Secondary parameters are C_{max} and C_{trough} at steady state.

In any PK study, anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points.

5.2. Pharmacodynamic studies

It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies whenever feasible. The PD markers should be selected on the basis of their relevance to the clinical outcome.

In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product, provided that the following conditions are met:

- The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, and euglycaemic clamp test to compare two insulins. Magnetic resonance imaging of disease lesions can be used to compare two β -interferons in multiple sclerosis.
- There may be PD-markers that are not established surrogates for efficacy but are relevant for the pharmacological action of the active substance and a clear dose-response or a concentration-response relationship has been demonstrated. In this case, a single or multiple dose-exposure-response study at two or more dose levels may be sufficient to waive a clinical efficacy study. This design would ensure that the biosimilar and the reference can be compared within the steep part of the dose response curve (assay sensitivity, see ICH topic E10).
- In exceptional cases, the confirmatory clinical trial may be waived if physicochemical, structural and *in vitro* biological analyses and human PK studies together with a combination of PD markers that reflect the pharmacological action and concentration of the active substance, can provide robust evidence for biosimilar comparability.

When evidence to establish clinical biosimilar comparability will be derived from PK studies supported by studies with non-surrogate PD/biomarkers, it is recommended to discuss such (“fingerprinting”) approach with regulatory authorities. The plan should include a proposal of the size of the equivalence margin(s) with its clinical justification as well as of the measures for demonstration of a comparable safety profile.

5.3. Efficacy trials

In the absence of surrogate markers for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, by using efficacy

endpoints. The study population should generally be representative of approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference. Occasionally, changes in clinical practice may require a deviation from the approved therapeutic indication, e.g. in terms of concomitant medication used in a combination treatment, line of therapy, or severity of the disease. Deviations need to be justified and discussed with regulatory authorities.

5.3.1. Study designs

In general, an equivalence design should be used. The use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship. A non-inferiority trial may only be accepted where the possibility of significant and clinically relevant increase in efficacy can be excluded on scientific and mechanistic grounds. However, as in equivalence trials, assay sensitivity has to be considered.

It is recommended to discuss the use of a non-inferiority design with regulatory authorities.

5.3.2. Efficacy endpoints

Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy *per se*, since this has already been established with the reference product. The purpose of the efficacy trials is to confirm comparable clinical performance of the biosimilar and the reference product.

CHMP has issued disease-specific guidelines for development of innovative medicinal products. In the development of a biosimilar medicinal product, the choice of clinical endpoints and time points of analysis of endpoints may deviate from the guidance for new active substances. Therefore, CHMP has issued product-class-specific guidelines to guide the development of biosimilar medicinal products in certain areas. In the absence of such a guideline, comparability should be demonstrated in appropriately sensitive clinical models and study conditions. The applicant should justify that the chosen model is relevant and sensitive to detect potential differences with regard to efficacy and safety. Nevertheless, deviations from endpoints recommended in disease-specific guidelines need to be scientifically justified. Differences detected between the efficacy of the biosimilar and reference products should always be discussed as to whether they are clinically relevant. Generally, the aim of clinical data is to address slight differences observed at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product. Clinical data cannot be used to justify substantial differences in quality attributes.

The correlation between the “hard” clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are more sensitive to detect clinically meaningful differences may have been demonstrated in previous clinical trials with the reference product. In this case, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorisation application of the reference product. However, it is advisable to include some common endpoints (e.g. as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product.

Comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical trials and CHMP guideline CPMP/EWP/2158/99 on the choice of the non-inferiority margin). As for all comparative clinical trial designs, assay sensitivity (see ICH topic E10) has to be considered.

5.4. Clinical safety

Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study. Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues known for the reference product. The duration of safety follow-up pre-authorisation should be justified. Care should be given to compare the type, severity and frequency of the adverse reactions between the biosimilar and the reference product, particularly those described in the SmPC of the reference product. The applicant should provide in the application dossier an evaluation of the specific risks anticipated for the biosimilar. This includes in particular a description of possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.

The principles for the assessment of immunogenicity of therapeutic proteins and monoclonal antibodies have been described in two CHMP guidelines (EMA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010). The potential for immunogenicity of a biosimilar should be investigated in a comparative manner to the reference product and should follow the principles as laid down in the aforementioned CHMP guidelines unless it can be justified that there is a need for deviation from this approach. The type and amount of immunogenicity data will depend on the experience gained with the reference product and the product class.

Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule which must meet all current standards. Analytical assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient. The analytical assays should preferably be capable of detecting antibodies against both the biosimilar and the reference molecule but should at least be able to detect all antibodies developed against the biosimilar molecule. Usually, the incidence and nature (e.g. cross-reactivity, target epitopes and neutralising activity) of antibodies and antibody titres should be measured and presented and should be assessed and interpreted in relation to their potential effect on clinical efficacy and safety parameters.

Duration of the immunogenicity study should be justified on a case-by-case basis depending on the duration of the treatment course, disappearance of the product from the circulation (to avoid antigen interference in the assays) and the time for emergence of humoral immune response (at least four weeks when an immunosuppressive agent is used). Duration of follow-up should be justified based on the time course and characteristics of unwanted immune responses described for the reference medicinal product, e.g. a low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity over time. In case of chronic administration, one-year follow up data will normally be required pre-authorisation. Shorter follow-up data pre-authorisation (e.g. 6 months) might be justified based on the immunogenicity profile of the reference product. If needed, immunogenicity data for an additional period, up to one-year, could then be submitted post-authorisation. For specific products, refer to product specific biosimilar guidance.

Increased immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, also a lower immunogenicity for the biosimilar is a possible scenario, which would not preclude approval as a biosimilar. In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This

subgroup analysis could be helpful to establish that the efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response.

6. Extrapolation of efficacy and safety from one therapeutic indication to another

The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by *in vitro* functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as

1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications
2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications
3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

7. Pharmacovigilance

Data from pre-authorisation clinical studies are usually insufficient to identify rare adverse effects. Therefore, clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.

Within the authorisation procedure the applicant should present a description of the pharmacovigilance system and a risk management plan in accordance with current EU legislation and pharmacovigilance guidelines. The risk management plan should take into account identified and potential risks associated with the use of the reference product and should detail how these issues will be addressed in post-marketing follow-up. Immunogenicity should specifically be addressed in this context. Any specific safety monitoring imposed on the reference medicinal product or product class should be adequately addressed in the pharmacovigilance plan of the biosimilar. Applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. However, new studies might have to be initiated. Risk minimisation activities in place for the reference medicinal product should, in principle, also be included into the risk management programme of the biosimilar. Any deviation from this (e.g. when the risk minimisation is linked to the device used with the reference product) should be justified.

For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all

appropriate measures should be taken to identify clearly any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number.