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4 Guideline on similar biological medicinal products 5 containing biotechnology-derived proteins as active 6 substance: non-clinical and clinical issues

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10 This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-
11 derived proteins as active substance: Non-clinical and clinical issues'
12 (EMEA/CHMP/BMWP/42832/2005).

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Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

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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* (EMEA/CHMP/BMWP/42832/05 Rev.1) lays down the non-clinical and clinical requirements for a biological medicinal product claiming to be similar to another one already marketed ("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 as well as the risk management plan with special emphasis on studying the immunogenicity of the biosimilar.

The current revision covers the following topics: a risk-based approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate endpoints in efficacy trials; design of immunogenicity studies; and extrapolation of indication.

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. A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy) based on a comprehensive comparability exercise.

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 together with the demonstration of comparability with the reference medicinal product by using appropriate physico-chemical and *in vitro* biological tests, non-clinical and clinical studies.

The quality issues relevant for demonstration of comparability for biosimilars containing recombinant DNA-derived proteins 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 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 has 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 licensed indications of the reference product and pathogenetic mechanisms involved in the disorders included in the therapeutic indications (e.g. mechanisms shared by various therapeutic indications).

The applicants 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, on one hand, and pharmacodynamics and clinical response, on the other hand. The availability of suitable biomarkers may abbreviate the (non-)clinical development. The safety profile of the reference product will determine the focus of the safety studies both pre- and post-marketing.

CHMP has issued product-class-specific guidelines to facilitate the (non-)clinical development of biosimilar medicinal products in certain areas. However, the applicants have to fine tune their (non-) clinical studies according to the results of preceding physico-chemical and *in vitro* biological analyses of the biosimilar and the reference product.

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 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).

3. Legal basis and relevant guidelines

Directive 2001/83/EC, as amended in particular in 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.

In addition, in particular, the following guidelines should be read in conjunction:

- Guideline on similar biological products (CHMP/437/04), 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)
- ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMEA/CHMP/ICH/731268/1998)
- 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)
- Guidelines on Good Pharmacovigilance Practices (GVP)
- ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- ICH E2E Note for guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)
- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/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 (EMEA/CHMP/EWP/192217/2009)
- Product-class-specific guidelines on various biosimilar products

4. Non-clinical studies

Non-clinical studies should be performed before initiating clinical trials. A step-wise approach should be applied to evaluate the similarity of biosimilar and reference product. *In vitro* studies should be conducted first and a decision then made as to the extent of what, if any, *in vivo* work will be required.

It is important to note that design of an appropriate non-clinical study program requires a clear understanding of the reference product characteristics. 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 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 could include relevant assays on:

- *Binding* to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects of the reference product.

- *Signal transduction and functional activity/viability* of cells known to be of relevance for the pharmaco-toxicological effects of the reference product.

The studies should be comparative in nature and should not just assess the response per se. The studies should evaluate parameters sensitive enough to detect differences. The studies should assess the concentration–activity/binding relationship between the biosimilar and the reference medicinal product covering a concentration range where differences are most sensitively detected. They should be performed with an appropriate number of batches of product representative of that intended for clinical use.

Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class. 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 comparability exercise.

The applicant should justify that the *in vitro* assays used are predictive for the *in vivo* situation.

If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development, should be considered instead.

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 relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).
- Significant quantitative differences in quality attributes between the intended 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 comparability exercise in the *in vitro* studies in step 1 is considered satisfactory and no factors of concern are identified in step 2, or these factors do not block direct entrance into humans, an *in vivo* animal study may not be 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. Applicants 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) should be considered when designing any *in vivo* study. Depending on the endpoints needed, 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 biotechnology-derived product and its clinical use.

When the model allows, the PK and PD of the biosimilar and the reference medicinal product should be quantitatively compared, including concentration-response assessment covering the therapeutic dose range 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.

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 will 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 quality differences 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 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, 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 comparability study with the test product derived from 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 bridging data.

The clinical 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 comparability.

5.1. Pharmacokinetic studies

Comparative 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 the 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* (EMEA/CHMP/EWP/192217/2009).

The criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, orally administered products may be acceptable in the absence of specific criteria for biologicals. Nevertheless, the comparability limits for the main PK parameters should be defined and justified prior to conducting the study.

For the demonstration of comparable pharmacokinetics, it is advisable to select the most sensitive test model. Healthy volunteers lack co-morbidity and co-medications and are likely to have less target-mediated clearance compared to patients. 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 high risk of immunogenicity.

PK studies are not always possible or feasible in healthy volunteers. In this case, the PK needs to be studied in patients. The most sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.

In certain cases, such as important target-mediated clearance, highly immunogenic proteins or highly variable PK parameters, it may be useful to collect additional PK data within the confirmatory efficacy clinical trial(s) as it 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. Anti-drug antibodies should be measured in parallel to PK assessment using the most appropriate sampling time points.

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 comparability in both absorption and elimination has been demonstrated for the subcutaneous route

In a single dose PK study, the primary parameters are the $AUC_{(0\text{-}inf)}$ for i.v. administration and $AUC_{(0\text{-}inf)}$ 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 ($AUC_{0\text{-}t}$) and AUC over a dosage interval at steady state ($AUC\tau$). Secondary parameters are C_{max} and C_{trough} at steady state.

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 clinical relevance.

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

- A clear dose-response relationship has been demonstrated. If not, the recommended study design is to conduct a multiple dose-exposure-response study. This design would ensure that the biosimilar and the reference can be compared within the linear ascending part of the dose response curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be sensitive but it cannot replace dose comparative studies.
- 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, euglycaemic clamp test to compare two insulins, and magnetic resonance imaging of disease lesions to compare two β-interferons.

The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of surrogacy is very rare. In such cases, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability.

When evidence to establish clinical comparability will be derived from studies with PD markers/biomarkers, it is recommended to discuss such approach with regulatory authorities. This should include a proposal of the size of the proposed equivalence margin and its clinical justification.

5.3. Efficacy trials

Usually, it is 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. The study population should 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 the clinical praxis mandate a deviation from the approved therapeutic indication, e.g. in terms of concomitant medication used as 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 increased 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 sole purpose of the efficacy trials is to investigate whether a clinically significant difference between the reference and biosimilar products can be detected.

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, the applicant should select the most sensitive endpoints. Nevertheless, deviations from disease-specific guidelines need to be scientifically justified. Differences detected should always be discussed as to whether they are clinically relevant.

The correlation between the “hard” clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are sensitive to detect differences may have been demonstrated in 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.

Clinical 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 clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered.

5.4. Clinical safety

Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety profile. 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 establishing comparability. Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues related to 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 related to infusion-related reactions and immunogenicity of the biosimilar that may result from a manufacturing process different from that of the reference product.

The principles for the assessment of immunogenicity of therapeutic proteins have been described in two CHMP guidelines (EMEA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010). The potential for immunogenicity of a biosimilar should always be investigated in a comparable 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 amount of immunogenicity data will depend on the reference product and/or the product class.

Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule. 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. Usually the incidence of antibodies and antibody titres should be measured and presented. 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 in case of an immunosuppressive agent). 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-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified based on the immunogenicity profile of the reference product. Immunogenicity data for the additional period, up to one-year, could then be submitted post-authorisation.

A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the biosimilar is also 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.

For biologicals with multiple indications, immunogenicity could differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified.

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

In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar 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, mechanisms of action of the active substance of the reference product in each indication (including its degree of certainty), and on receptors involved. Binding of the reference substance to the same receptors may have different effects in different target cells depending on differences in the intracellular signalling pathways, e.g. due to transformation. This situation is not an argument for additional studies. However, if there is evidence that different active sites of the reference product or different receptors of the target cells are involved in different therapeutic indications or that the safety profile of the product differs between the therapeutic indications, additional data may be needed to justify the extrapolation of safety and efficacy from the indication studied in the pivotal clinical trial. For the extrapolation of safety, the Applicant should consider patient-related factors, such as different co-medication, co-morbidities, and immunological status, and disease-related factors, such as reactions related to the target cells, e.g. lysis of tumour cells. The extent of such data should be considered in the light of the totality of evidence derived from the biosimilar comparability exercise and the potential remaining uncertainties.

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, if applicable, additional potential risks identified during the development programme of the biosimilar and should detail how these issues will be addressed in post-marketing follow-up. Immunogenicity should specifically be addressed in this context. Within the pharmacovigilance plan, any specific safety monitoring imposed on the reference medicinal product or product class should be taken into consideration. Applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. Risk minimisation activities in place for the reference medicinal product should also be included into the risk management programme of the biosimilar.

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 the name of the medicinal product and the batch number.

Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, ‘switching’ and ‘interchanging’ of medicines that contain a given biological might occur. Thus, applicants are recommended to follow further development in the field and consider these

aspects as part of the risk management plan. In addition, available data on switching should be carefully assessed during the review of adverse reaction reports.

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