EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2010
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies

Draft

Draft Agreed by Similar Biological Medicinal Products Working Party	**October 2010**
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011

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

Keywords	***Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, clinical use, clinical endpoints, extrapolation***

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies

Table of contents

Executive summary

This guideline lays down the non-clinical and clinical requirements for monoclonal antibody (mAb) containing medicinal products claiming to be similar to another one already marketed. The non-clinical section addresses the pharmaco-toxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance aspects.

As regards non-clinical development, a risk-based approach to evaluate mAb on a case-by-case basis is recommended to decide on the choice and extent of *in vitro* and *in vivo* studies. *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. If an *in vivo* study is deemed necessary, the focus of the study (pharmacokinetics, pharmacodynamics, and/or safety; normally comparative in nature) depends on the need for additional information, and the availability of a relevant animal model. The conduct of large comparative toxicological studies in non-human primates is not recommended. As regards clinical development, a comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population (healthy volunteers or patients) normally forms an integral part of biosimilar mAb development, usually in a parallel group design due to the long half-life of mAbs and potential interference of immunogenicity. The design of a pharmacokinetic study will depend on various factors, including clinical context, linear versus non-linear pharmacokinetics etc. Pharmacokinetic data can be helpful to extrapolate data on efficacy and safety between different clinical indications of the reference mAb. It may, on a case-by-case basis, be necessary to undertake multidose pharmacokinetic studies in patients, or even to perform pharmacokinetic assessment as part of the clinical study designed to establish similar efficacy and safety. Pharmacokinetic studies can be combined with pharmacodynamic (PD) endpoints, where available. Sponsors should always explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity. Normally, similar clinical efficacy should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, normally equivalence trials. To establish biosimilarity, deviations from disease-specific guidelines issued by the CHMP (for example, choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. The focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se, which has already been shown for the reference product. In principle, the most sensitive model and study conditions (pharmacodynamic or clinical) should be used in a homogeneous patient population, since this reduces variability and thus the sample size needed to prove similarity, and can simplify interpretation. In cases where comparative pharmacodynamic studies are claimed to be most suitable to provide the pivotal evidence for similar efficacy, Applicants will have to choose clinically relevant markers and also provide sufficient reassurance of clinical safety, particularly immunogenicity. It may be difficult to define an appropriate equivalence margin for pharmacodynamic equivalence based on clinical relevance, and to provide reassurance that all relevant aspects of a biosimilar mAb as regards similar clinical efficacy are covered. Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity. Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the results of the overall evidence provided from the biosimilarity exercise and with adequate justification. As regards post-authorisation follow-up, the concept to be proposed by Applicants may have to exceed routine pharmacovigilance, and may have to involve more standardized environments.

1. Introduction

Monoclonal antibodies have been established as a major product class of biotechnology-derived medicinal products. Different mAb products share some properties, e.g. being cytotoxic to their target, or neutralizing a cytokine, but differ in aspects like the mechanism of action. On one hand, they are structurally complex, and may have several functional domains within a single molecule, depending on the isotype (antigen-binding region, complement-binding region, constant part interacting with Fc receptors). Each individual mAb may present a unique profile with respect to the criticality of the antigen-binding region, the Fc cytotoxic effector function, and binding to Fc receptors including FcRn. On the other hand, various assays have been established in the past years that allow for more in-depth characterisation of complex proteins, both on a physicochemical and a functional level, e.g. with potency assays. However, it may at the current stage of knowledge be difficult to conclude on the relevance of minor quality differences in the physicochemical and biological characterization. Nevertheless, such mAbs are being developed, and CHMP has given scientific advice for the development of some individual products. This guideline lays down the non-clinical and clinical requirements for monoclonal antibody-containing medicinal products claiming to be similar to another one already marketed, i.e. similar biological medicinal products (biosimilars).

For quality aspects the principles as laid out in the comparability guidelines including the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CHMP/ 49348/05) and the "Guideline on production and quality control of monoclonal antibodies and related substances" (CHMP/BWP/157653/07) apply. Although specific considerations as regards quality of biosimilar mAbs are important, these are relevant in a more general context and will thus be implemented in a revision of the Guideline EMEA/CHMP/49348/05 (see concept paper published at EMA website).

2. Scope

The "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CPMP/42832/05/) lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. This product specific guidance complements the above guideline and presents the current view of the CHMP on the application of the guideline for demonstration of biosimilarity of two mAb-containing medicinal products. While this guidance is specifically related to mAbs, the principles discussed may also, on a case-by-case basis, be relevant for related substances like for example fusion proteins based on IgG Fc (-cept molecules).

Second- or next-generation biologicals, defined as biologicals that are structurally and/or functionally altered, in comparison to already licensed reference products, to gain an improved or different clinical performance, are beyond the scope of this guideline. Nevertheless, principles laid down in this guideline could apply on a case-by-case basis. In these cases Sponsors are recommended to seek scientific advice from the European Medicines Agency, or from national competent authorities.

3. Legal basis

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.

4. Non-clinical studies

A risk-based approach to evaluate mAb on a case-by-case basis is recommended.

Non-clinical studies should be performed before initiating clinical development. *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.

The approach taken will need to be fully justified in the non-clinical overview.

4.1. In vitro pharmacodynamic (PD) studies = step1

In order to assess any difference in biological activity between the similar biological medicinal 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 be provided.

In vitro non-clinical studies should include relevant studies on:

- Binding to the target antigen
- Binding to all Fcgamma receptors, FcRn and complement
- Fab-associated functions (e.g. neutralization, receptor activation or receptor blockade)
- Fc-associated functions (ADCC and CDC assays, complement activation)

These concentration/activity studies should be comparative in nature and should be designed to exclude all differences of importance in the concentration – activity relationship between the similar biological medicinal product and the reference medicinal product and should not just assess the response per se.

Together these assays should cover all functional aspects of the mAb even though some may not be considered necessary for the mode of action in the clinic. As these assays may be more specific and sensitive than studies in animals, these assays can be considered fundamental in the non-clinical comparability exercise. It is acknowledged, however, that some mAbs may mediate effects in vivo in ways that are not yet fully elucidated.

4.2. Identification of factors of importance for the in vivo non-clinical strategy = step 2

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

- Differences in process-related impurities due to a different cell expression system compared with the reference medicinal product (e.g. yeast, insect, plant, vs. mammalian expression system).
- The presence of a mixture of product- and/or process related impurities that can be less well characterized.
- Significant differences in formulation, use of not widely used excipients.
- The need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers
- Availability of a relevant in-vivo model (with regard to species or design, e.g. transplantation models) which is likely capable of providing interpretable data on similar in vivo behaviour of biosimilar and reference mAb.

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

4.3. In vivo studies = step 3

If the comparability exercise in the *in vitro* PD studies in step 1 is considered satisfactory and no factors of concern are identified in step 2, an *in vivo* animal study is not considered necessary.

If the outcome of steps 1 and 2 raises concerns, the need for comparative *in vivo* studies should be decided case-by-case.

If an *in vivo* study is deemed necessary, the focus of the study (PK, PD and/or safety) depends on the need for additional information. Animal studies should be designed to maximise the information obtained, and safety and PD endpoints may be included in a PK study if considered appropriate and feasible.

The possibility of performing *in vivo* comparative PK and PD studies depends on the characteristics of the product, and on the availability of a relevant animal species, or other relevant models (e.g. transgenic animals or transplant models) and their sensitivity. Such model would have to allow for quantitative comparison of PK and PD of the similar biological medicinal product and the reference medicinal product, including dose-response assessment covering a therapeutic dose in humans.

Due to the specificity of mAbs, the relevant species for toxicology studies is in most cases a non-human primate. The conduct of large comparative toxicological studies in non-human primates is not recommended. If safety testing in vivo is needed in non-human primates, the use of only one dose and one gender and omission of a recovery group might be justified. In principle, the toxicology study should be comparative in nature, unless scientific justification can be provided to indicate that a direct comparison is unnecessary. The duration of the study should be justified, taking into consideration the PK behaviour of the mAb and the clinical posology.

The conduct of toxicity studies in non-relevant species (i.e. only to assess unspecific toxicity, based on impurities) is not recommended.

Immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, but may be needed for interpretation of PK studies and toxicity findings (or lack thereof). Blood samples should be taken and stored for future evaluations if then needed.

Local tolerance endpoints should only be included in an in vivo study if there is a special need for additional information.

Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of similar biological medicinal products containing monoclonal antibodies as active substance.

5. Clinical Studies

5.1. Pharmacokinetics (PK)

5.1.1. Study design

The comparison of the pharmacokinetic properties of the similar biological medicinal product and the reference product form an integral part of biosimilar mAb development. A parallel group design is acceptable due to the long half-life of monoclonal antibodies and the potential influence of immunogenicity. Clearance may change significantly after a first dose, hence therapeutic response and

severity of the disease can affect PK. In such cases, in principle, a single dose PK evaluation is most sensitive. However, for the design of a PK study for a biosimilar mAb, particulars like the clinical context will have to be taken into account. The design of the study depends on the PK characteristics of the antibody (linear or non-linear PK, time-dependencies) and should take into account the recommendations as outlined in the "Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins" (CHMP/EWP/89249/2004).

5.1.2. Selection of a sensitive population

The primary objective of the pharmacokinetic studies performed to support a Marketing Authorisation Application (MAA) for a similar biological medicinal product is to show comparability in pharmacokinetics of the biosimilar with the reference product in a sufficiently sensitive and homogeneous population. Choice of a homogeneous population is expected to reduce variability and thus the sample size needed to prove equivalence, and can simplify interpretation.

Single dose studies may be possible in healthy volunteers with adequate justification, depending on the mAb. For mAbs licensed in several clinical indications, it is not generally required to investigate the pharmacokinetic profile in all of them. However, if distinct therapeutic areas are involved for one particular mAb (e.g. autoimmunity and oncology), separate PK studies may be recommendable as a support for extrapolation between these indications. Applicants should focus on the patient population where pharmacokinetic equivalence to the reference mAb can be studied with sufficient sensitivity. The choice of the patient population should be fully justified, based on a comprehensive survey of scientific literature, as regards sensitivity, and also the possibility to infer PK results to the other clinical indications where the reference mAb is licensed. Factors that may influence the choice of the patient population are age of usual manifestation and age range (since lower age may be less prone to presence of concomitant clinical conditions), number of previous treatments, concomitant treatments, or expression of antigen (which may be related to disease stage). Another factor is the dosage regimen in different populations: In case of nonlinear PK with overproportional increase, a comparison in the population with the highest dosage regimen would be advisable.

It may be necessary to perform the PK study in a different patient population than the clinical trial designed to establish similar clinical efficacy, since the population where PK is measured most sensitively may not be the same as the population where similar efficacy and safety can be measured most sensitively. In such scenarios, population PK measurements of sampling during the phase III study are recommended as additional information, since such data may add relevant data to the overall database to claim biosimilarity, and may support extrapolation between indications.

5.1.3. Multidose PK and endpoints

If a multidose PK study in patients is performed, sampling should normally be undertaken after the first dose and later, preferably at steady state. The preferred PK endpoints may depend on the type of mAb and on the known PK characteristics (linear or non-linear PK). Usually employed primary parameters are AUC, Cmax, and Ctrough in determinations at steady state. Other PK parameters like clearance and half-life should be determined and reported in a descriptive manner. If relevant differences occur the assumption of similar PK might be seriously questioned. If such results are observed, it is recommended to consult regulatory authorities on the further proceeding of a biosimilar mAb development.

PK investigations both after the first dose and at a later dose interval (steady state) should be considered in light of the long loading dose interval and long half-life of mAbs and, especially in case of nonlinear PK of the reference mAb. In such case (e.g. many cytotoxic mAbs with cellular targets), clearance and half-life are concentration (dose) dependent. This dependency has impact on steady

state levels. In these cases PK comparison of steady state levels after multiple dosing are considered most appropriate (AUC_{ss}, $Cmax_{ss}$, $Ctrough_{ss}$). Concentration-, time-dependent or immunogenicity-related changes in distribution or elimination kinetics may occur leading to differences in PK after repeat administration. Thus, anti-drug antibodies should be measured in parallel.

Equivalence margins have to be defined a priori and appropriately justified. For some mAbs, inter-subject variability for some parameters was reported to be considerable. This may have to be accounted for in the choice of the equivalence margin at least for such parameters. As a principle, any widening of the conventional equivalence margin beyond 80-125% requires thorough justification, including an estimation of potential impact on clinical efficacy and safety. This should be discussed with regulatory authorities. Of note, these studies are undertaken with the aim to exclude differences in the PK behaviour of the biosimilar. A significant difference, yet fulfilling equivalence criteria, may indicate potential differences in the interaction between the target antigen(s) and the biosimilar mAb, and thus may question the biosimilarity concept.

Usually, proof of similar PK profiles should precede clinical trials. However, in certain scenarios, e.g. for mAbs where PK is inevitably highly variable even within one clinical indication, it may, for feasibility reasons, be necessary to explore PK comparisons as part of a clinical study that is designed to establish similar clinical efficacy (as only this trial will then be large enough to demonstrate PK equivalence). In this case an exploratory PK study with the objective of investigating tolerability and obtaining an initial trend for evidence of pharmacokinetic equivalence applying a preliminary and less stringent equivalence requirement as a stop/go indicator before commencing the comparative clinical efficacy trial should normally be performed. To start with a comparative clinical efficacy trial that includes PK, without formal phase I study, could also become problematic, as there was no former exposure of humans to the biosimilar mAb, together with potentially limited non-clinical data, depending on the mAb. If the PK and PD biosimilarity exercise is to be included into the clinical efficacy trial, proper measures have to be pre-planned to ensure the statistical rigour and integrity of this trial. It is recommended that such concepts are discussed with regulatory authorities before commencing such a trial. It will be necessary to consider the objective of the interim analysis on PK parameters (to exclude large differences in PK such that it would be unsafe or unethical to continue the study, or to establish PK equivalence), access to unblinded PK data, which usually need not include sponsor personnel or trial investigators, and whether design modifications might be envisaged (including additional interim analyses). A design in which PK data are analysed and interpreted by an independent monitoring committee without treatment allocation being revealed to sponsors and investigators could be accepted.

5.1.4. Additional considerations for PK measurements of cytotoxic mAbs in anticancer indications

Pharmacokinetics of anticancer (cytotoxic) mAbs may be time dependent, as the tumour burden may change after multiple dosing (in case of response increase of half-life with multiple dosing). This should be taken into account in the design of the study and statistical analyses. For mAb targets that involve receptor shedding, it is advisable to measure shed receptor levels at baseline and, if relevant, during the conduct of the study, in order to verify the baseline comparability of the treatment groups and to generate helpful additional data. An exploratory statistical analysis, if possible, on post-baseline comparability at the timepoint relevant to the conclusion of PK equivalence could be helpful.

When several therapeutic regimens are licensed for a reference mAb, the comparative pharmacokinetic study between biosimilar and reference mAb should be designed to demonstrate clinical comparability selecting the most sensitive key PK parameters. Subject to reasonable justification, there is no need to test all therapeutic dose regimens. Similar considerations apply for mAbs which are indicated for both,

monotherapy and in combination with chemotherapy. It is usually recommended to study the comparative PK in the monotherapy setting in order to minimize sources for variability, although chemotherapy often does not significantly alter PK characteristics.

With regard to the "model" indication for a comparative PK study, an adjuvant setting in patients with early cancer, if possible, may be advisable, since the tumour burden is low. However, clearance due to mAb-antigen interaction will not be captured. Thus, the choice of the population should be justified accordingly.

5.2. Pharmacodynamics (PD)

Pharmacokinetic studies can be combined with pharmacodynamic (PD) endpoints, where available. With regard to pharmacodynamic evaluation, there is often a lack of specific PD endpoints. Therefore, the emphasis will often be on non-clinical PD evaluations, e.g. *in-vitro* testing.

Sponsors should always explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity. A single or repeat dose study in the saturation part of the dose-concentration-response curve is unlikely to discriminate between different activities, should they exist. Thus, PD data from lower dose(s) may, in principle, provide already pivotal information for the biosimilarity exercise. It is acknowledged that dose-response data may not exist for the reference mAb, and that exposing patients to a relatively low dose of the mAbs, in a worst case scenario, might sensitize them to develop anti-mAb antibodies, and, consequently, may make them treatment resistant. However, for some reference mAbs clinical conditions may exist where such studies are feasible. It may be more challenging to define an appropriate equivalence margin for establishing equivalent efficacy based on PD markers than on clinical endpoints. Applicants will have to provide reassurance that all relevant aspects of a biosimilar mAb as regards similar clinical efficacy are covered. In particular, where different mechanisms of action are relevant for the claimed indication(s) of the reference product, or uncertainty exists, Applicants should provide relevant data to cover pharmacodynamics for all claimed clinical indications. In such cases, the sponsor should seek for scientific advice for study design and duration, choice of doses, efficacy / pharmacodynamic endpoints and their relevance as regards clinical meaningfulness, and comparability margins.

5.3. Clinical Efficacy

If dose comparative and highly sensitive PD studies cannot be performed convincingly showing comparability in a clinically relevant manner, similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blinded and normally equivalence trials.

With regard to the specific issues with equivalence trials, e.g. assay sensitivity, reference is made to guideline ICH E10 and the "Guideline on the choice of the non-inferiority margin". For most of the clinical conditions that are licensed for mAbs, specific CHMP guidance on the clinical requirements exists. However, to establish biosimilarity, deviations from these guidelines (choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. Such deviations need to be fully scientifically justified. In such circumstances it is recommended, where feasible, to include the usually recommended endpoints for a certain condition as secondary endpoint. An alternative could be to provide an acceptable interim endpoint for licensing and, should the usually recommended endpoint not feasibly be reached within the pivotal study, data on this endpoint could be gathered in a post-authorisation setting, where feasible and considered necessary. However, such data would have to be interpreted with caution, due to numerous influencing factors and likely imprecise estimates.

Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not), and the applicant should justify that the model is relevant and sensitive to demonstrate comparability in relation to efficacy and safety in the indication(s) applied for. It is recommended that such approach is discussed upfront with regulatory authorities, e.g, via CHMP Scientific Advice. In principle, the most sensitive clinical model should be used in a homogeneous patient population, since this reduces the variability and thus the sample size needed to prove equivalence, and can simplify interpretation. For example, patients with different disease severity and with different previous lines of treatment might be expected to respond differently, and thus differences between the study arms may be difficult to interpret, and it may remain uncertain whether such differences would be attributable to patient or disease related factors rather than to differences between the biosimilar mAb and reference mAb. The safety of patients should not be compromised by a biosimilarity exercise, and patients should only be treated as medically indicated.

Clinical studies in special populations like the paediatric population or the elderly are normally not required since the overall objective of the development programme is to establish biosimilarity, and therefore the selection of the primary patient population is driven by the need for homogeneity and sensitivity.

The inclusion of patients from non-European countries is generally possible. Knowledge of efficacy and safety of the reference mAb in a particular region may be necessary in order to prospectively define an equivalence margin. Stratification and appropriate subgroup analyses are normally expected if patients from different global regions are included. Diagnostic and treatment strategies should be comparable in order to prevent the influence of extrinsic factors.

5.3.1. Additional considerations for mAbs licensed in anticancer indications

Establishing similar clinical efficacy and safety of biosimilar and reference mAb may be particularly challenging in an anticancer setting: According to the "Guideline on the evaluation of anticancer medicinal products in man" (CHMP/EWP/205/95/Rev.3/Corr.2) the preferred endpoint to prove efficacy in cancer indications would be either progression free / disease free survival (PFS / DFS) or overall survival (OS). Such endpoints are important to establish patient benefit for a new anticancer drug, but may not be feasible or sensitive enough for establishing biosimilarity of a biosimilar mAb to a reference mAb, since they may be influenced by various factors not attributable to differences between the biosimilar mAb and the reference mAb, but by factors like tumour burden, performance status, previous lines of treatments, underlying clinical conditions, subsequent lines of treatment (for OS), etc. They may therefore not be suitable to establish similar efficacy of the biosimilar and the reference mAb.

The focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit *per se*, which has already been established by the reference product. Therefore, in general the most sensitive patient population and clinical endpoint is preferred to be able to detect product-related differences, if present and, at the same time, to reduce patient and disease-related factors to a minimum in order to increase precision. A clinical trial in a homogeneous patient population with a clinical endpoint that measures activity as primary endpoint may be considered. An example may be Overall Response Rate (ORR, proportion of patients in whom a Complete Response (CR) or Partial Response (PR) was observed). It may also be worthwhile to explore ORR measured at a certain timepoint (i.e., ORR at x months) or percentage change in tumour mass from baseline instead ("waterfall plot"). Applicants should engage in efforts for a standardized assessment with patients evaluated at appropriate intervals. PFS and OS should be recorded, where feasible. In case PFS is likely to be more sensitive than ORR as outcome measure, this is the preferred option even though this will prolong the clinical study. It is acknowledged that data on survival may

have to be interpreted with caution due to numerous factors influencing survival beyond the performance of the biosimilar mAb or the reference mAb.

Novel endpoints may be employed on an exploratory basis if well justified (e.g., time to response).

5.4. Clinical Safety

Clinical safety is normally studied as part of the clinical study to establish similar efficacy of biosimilar and reference mAb. It is recommended to use the same definitions for safety parameters as that used for the reference mAbs in its original development programme (if known) where no homogeneous definition exists (e.g., measurement of cardiotoxicity). Comparable safety with respect to pharmacologically mediated adverse reactions (e.g., cardiotoxicity) should also be considered as a measure of biosimilarity. In cases where comparative and highly sensitive PD studies are suitable to provide the pivotal evidence for equivalence in clinical efficacy, Applicants will have to provide sufficient reassurance of clinical safety, including immunogenicity. Prelicensing safety data should be obtained in a number of patients sufficient to determine the adverse effect profiles of the biosimilar medicinal product. Care should be given to compare the type, frequency and severity of the adverse reactions between the similar biological medicinal product and the reference product, with focus on the adverse reactions described for the reference product.

Rare events such as progressive multifocal leukencephalopathy are unlikely to be detected in a pre-authorisation setting. Therefore, Applicants need to propose pharmacovigilance and risk management activities for the post-authorisation phase at the time of the marketing authorisation application (see chapter in this guideline). Usually, similar pharmacovigilance activities as those of the reference product would be required, rather than a direct comparison with the reference product, since data will most likely be difficult to interpret due to their rarity of occurrence.

When designing their development programme, sponsors should reflect upon how re-treatment of patients would be handled. Concepts should be presented at the time of marketing authorisation application on how to systematically measure safety of repeat exposure of patients, for example in oncological indications where patients undergo several treatment cycles. It may be advisable to extend the clinical study as a post-authorisation follow-up study to a full treatment cycle, where relevant and feasible.

As regards immunogenicity assessment, Applicants should refer to existing CHMP guidance. Systematic evaluation and discussion of immunogenicity is important, due to clinical consequences like loss of efficacy and also likely resistance against further treatment with the reference mAb. It is recommended to exclude patients previously treated with the reference mAb where possible as this could hamper interpretation of the safety data and thus also decrease sensitivity for detecting differences. Study of unwanted immunogenicity is especially important when a different expression system is employed for the biosimilar mAb compared to the reference mAb, particularly if there is limited experience with this expression system in humans. It is recommended that such approaches are discussed in advance with regulatory authorities.

Additional long-term immunogenicity and safety data might be required post-authorisation, e.g. in situations where the study duration for establishing similar clinical efficacy is rather short. As regards safety across different indications licensed for the reference mAb and claimed by the biosimilar mAb, a post-authorisation concept for obtaining further indication-specific safety data may be needed.

6. Extrapolation of Indications

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. If pivotal evidence for biosimilarity is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then Applicants should provide relevant data to cover pharmacodynamics for all claimed clinical indications. Applicants should support such extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action.

If a reference mAb is licensed both as an immunomodulator and as an anticancer (cytotoxic) antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging. The basis for such extrapolation forms an extensive quality and non-clinical database, including potency assay(s) and in-vitro assays that cover the functionality of the molecule. The possibility of extrapolating safety including immunogenicity data also requires careful consideration. For the mechanism of action, e.g. the depletion of immune cells, several mechanisms may play a role, and at the present stage of knowledge it cannot be assumed that the same mechanisms of cell depletion are of the same importance in different disease states. Antibody-dependent cytotoxicity (ADCC) appears to be more important in some indications than in others. To provide further evidence about the mechanism of action, it may also be helpful to perform a literature search to identify what is known about potential signalling inhibition by the reference mAb that would not be covered by ADCC/CDC tests, in particular direct induction of apoptosis. This could provide more knowledge on potential read-outs that could be used to support biosimilarity on a molecular level.

7. Pharmacovigilance Plan and Post-authorisation Follow-up

For the marketing authorisation procedure the applicant should present a risk management programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines.

Further to safety considerations as discussed above, Applicants should provide at the time of MAA a comprehensive concept how to further study safety in a post-authorisation setting including also the following aspects:

- Safety in indications licensed for the reference mAb that are claimed based on extrapolation of efficacy and safety data.
- Occurrence of rare and particularly serious adverse events described for the reference mAb.
- Detection of novel safety signals, as for any other biological medicinal product.

The concept may have to exceed routine pharmacovigilance, and may have to involve more standardised environments. In addition, participation in already existing registries should be explored and presented as part of the Risk Management Plan. The adequacy of such proposals will have to be assessed in the context of the safety data at the time of approval, the overall data from the biosimilarity exercise, and the known safety profile of the reference mAb.

Applicants are recommended to follow further developments in the field of handling of biosimilars and reference medicinal products in clinical practice. Recommendations like recording the brand name of the drugs used by physicians, could be taken into account to reinforce traceability.

8. References

Directive 2001/83/EC, as amended

Guideline on similar biological medicinal products (CHMP/437/04)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005)

Guideline on production and quality control of monoclonal antibodies and related substances (CHMP/BWP/157653/07)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05).

Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/ 2145/00).

Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)

Note for guidance for toxicokinetics: A guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95)

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004).

Guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95/Rev.3/Corr.2)

ICH E10 Choice of Control Group in Clinical Trials CPMP/ICH/364/96

Guideline on the choice of a non-inferiority margin CPMP/EWP/2158/99

Extrapolation of results from clinical studies conducted outside Europe to the EU-population CHMP/EWP/692702/08

Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (CHMP/BMWP/14327/06)

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)