30 May 2012
EMA/205886/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on similar biological medicinal products containing monoclonal antibodies' (EMA/CHMP/BMWP/403543/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Immunogenicity Platform vzw (EIP)
2	Swissmedic, Swiss Agency for Therapeutic Products
3	Statisticians in the Pharmaceutical Industry (PSI)
4	The Medicines Evaluation Board (MEB-NL)
5	The Janssen Pharmaceutical Companies of Johnson & Johnson
6	German Association of Research-Based Pharmaceutical Companies (vfa)
7	The UK BioIndustry Association (BIA)
8	Società Italiana di Farmacologia (Italian Society of Pharmacology)
9	Novartis Pharma AG, Basel, Switzerland
10	Elan Pharma International Ltd
11	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
12	International Psoriasis Council (IPC)
13	Mr Malik Osmane
14	Novartis International AG (including Sandoz International GmbH and Novartis Pharma AG)
15	Pfizer, Inc.
16	Synthon BV
17	European Generic medicines Association (EGA)
18	Società Italiana di Ematologia (SIE) and Fondazione Italiana Linfomi (FIL)
19	LFB-Biotechnologies
20	European Biopharmaceutical Enterprises (EBE)
21	F. Hoffmann-La Roche Ltd.
22	The Biotechnology Industry Organization (BIO)

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Many comments were repetitive or even identical. BMWP did in those cases not repeat their comment.

1. General comments – overview

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1	This is a very clear, thoughtful and forward-looking draft guideline for an important class of biosimilars. It is a clear next step in the thinking about how to develop biosimilar monoclonal antibodies and it confirms the leading position of the EMA/CHMP. The guideline is well written and comprehensive. As the European Immunogenicity Platform, (www.E-I-P.eu) acts as a central meeting place for European biopharmaceutical companies and scientific experts active in the field of immunogenicity, these submitted comments are more or less restricted to immunogenicity.	
2	The draft document is very mature and well written. It covers all important areas. There are a few general comments: I.) Some text on validation of the bioassay measuring binding of the antibody to the target antigen should be added, since usually binding to the target antigen is done in a sandwich technique and the capturing antibody needs to be characterized for its performance in the assay. The discriminative power of the assay needs to be analyzed. Usually in a solid phase assay large variations in affinity are possible. II.) There is some inconsistency between 5.2 Pharmacodynamics and 5.3 Efficacy that leave much room for speculation The first sentence in 5.3 saying "if dose comparative and highly sensitive PD studies cannot be performed convincingly showing	It is agreed that the quality of the assays used should be adequate. The choice of the assay is up to the Applicant. The validity and adequacy of the data will be assessed when received. Sections 5.2 and 5.3 have been revised.

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	comparability in a clinically relevant manner" is not clear. It is not defined in 5.2 what a highly sensitive PD study would be. There is no mentioning of validation, surrogate biomarker, assay methodology or at least correlation to clinical endpoints. Therefore, the reader assumes that in general a PD study would be sufficient evidence for biosimilarity, but in reality this is not the case, since this "comparability in a clinically relevant manner" is not feasible. III) There is some repetitiveness between section which might be unavoidable, but repetition of identical sentences is unnecessary.	
4	This is a very clear, thoughtful and imaginative draft guideline for an important class of biosimilars. It is a clear next step in the thinking about how to develop biosimilar monoclonal antibodies and it confirm the leading position of the EMA/CHMP Within section 7 there should also be mentioned that risk minimisation activities in place for the reference product should be discussed in the RMP of the biosimilar and if considered necessary, these should also be applied for the biosimilar. Regarding the non-clinical section we very much support the introduction of a risk-based tiered approach. We believe that in most – if not all - cases the clinical experience with the reference product together with the comparative quality and non-clinical *in vitro* data will obviate the need for *in vivo* studies, which can not be comparative in nature, unless a large number of animals would be sacrificed. Therefore, an opinion on the acceptability of the use of a biosimilar mAb in a clinical trial should be based on the comparative quality and non-clinical *in vitro* data and an opinion on the biosimilarity of the	The need for risk minimisation activities has been included in section 7.

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	biosimilar mAb after an MAA has been received should be based on the same data together with the clinical data obtained with the biosimilar mAb. Here we would like to make reference to the position paper published on the website of the MEB, and which has been added to this document as an attachment.	
5	The Janssen Pharmaceutical Companies of Johnson & Johnson (Johnson & Johnson) are among the global leaders in biotechnology and have many years of experience with the development and manufacture of biopharmaceutical products, including monoclonal antibodies (mAbs). We developed OKT3 (muronomab-CD3), the first commercial therapeutic antibody, approved in June 1986 in both the United States and Europe (France), for the inhibition of transplanted organ rejection. We also developed and manufacture ReoPro® (abciximab), REMICADE® (infliximab injection), SIMPONI® (golimumab), and Stelara™ (ustekinumab). These products cover a broad range of therapeutic areas and are prescribed to patients in over 100 countries around the world. Johnson & Johnson thus has extensive experience with the many complex issues raised by mAbs. A substantial concern with the draft guideline is that it does not address the quality aspect of a monoclonal antibody (mAb) biosimilar development program. It is therefore unclear how structurally similar the CHMP will require a proposed biosimilar and reference product to be. We understand that the focus of the draft guideline is the non-clinical and clinical programs for biosimilar mAbs. The scope and design of the non-clinical and clinical programs depend, however, on the degree and nature of structural differences between the products— whether identified or simply not excluded by analytical and	As stipulated by the respondent, there is a lot of emphasis in the non-clinical section to establish similar biological activity. This and at least 10 years of clinical experience with the innovator product would preclude the occurrence of new unexpected toxicity with the biosimilar detectable with a toxicology study. Consequently, we disagree that more emphasis should be placed on toxicology. Quality aspects were discussed and put to the initial internal draft, but it was decided that what was written was relevant to all biosimilars, not only to mAbs. Therefore, the general quality guideline is currently updated. Moreover, it is not possible to determine in a general guideline the degree of

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	non-clinical testing. For this reason, we believe the CHMP must address the quality aspect of a mAb biosimilar development program before it finalizes the guideline on non-clinical and clinical testing. We therefore recommend that this guideline state explicitly that a proposed biosimilar mAb must be highly similar in structure to the reference product. Moreover, it is not sufficient to require that the reference product and proposed biosimilar have the same complementarity determining regions and epitope binding properties and sites. The products should have the same primary structures, secondary and tertiary structures, and functional domains. Further, the proposed biosimilar must be as similar to the reference product as is reasonably achievable, including with regard to post-translational modifications. Every difference between the products carries with it the potential for undetected clinical risk, so any differences that can reasonably be eliminated constitute avoidable risk and should be prohibited. In particular, we are concerned that the guideline appears to permit significant differences between a biosimilar mAb and its reference product, including changes in formulation and host cell expression systems. These changes would serve no public health purpose, would raise safety and efficacy risks, and could allow biosimilar applicants to deliberately circumvent an innovator's patents. The non-clinical section of the draft guideline appropriately focuses on the need to identify and exclude differences between the reference product and the proposed biosimilar. It should also make clear that the goal of the non-clinical program is to ensure that the products share as many physiochemical and biological characteristics as possible. The CHMP should note that some differences with clinical significance may not be detectable in the non-clinical program. Finally, we recommend that the non-clinical section of the draft	similarity that a biosimilar should have, since it depends on the mAb in question, the methods applied, the expression system used, the in-vitro data obtained etc. It will be the overall data package that will determine the acceptability of a biosimilar mAb as a biosimilar. Nevertheless, a sentence has been added to the Introduction that a biosimilar is expected to be highly similar. The guideline was never meant to allow for more than minor and non-functionally relevant differences.

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	guideline place much greater emphasis on the need for toxicology testing. In our view, a biological product should never be administered to humans without *in vivo* toxicology data. The CHMP should require at least one repeat-dose toxicology study in a relevant species before any biosimilar mAb is administered to a human. The nature (i.e., comparative or noncomparative) and extent (i.e., multiple dose levels or single dose level) of the studies should be determined on a case-by-case basis. The draft guideline appropriately recommends that biosimilar applicants use a risk-based approach when designing their development programs. In the early stages of the biosimilar development program, however, applicants may have insufficient experience with and information about the product to adequately identify and assess the relative importance of any risks for this purpose. It is important that applicants not bypass essential non-clinical testing. The CHMP should always require at least one toxicology test and appropriate *in vitro* testing for a biosimilar. After this minimum level of testing is completed, a risk-based approach can help to determine what additional non-clinical and clinical tests are needed. A risk-based approach should not, however, lead to a significant reduction in preauthorization testing as compared to what has been required for other biosimilars to date. In addition, the CHMP and applicants currently have little experience with biosimilar mAbs. A cautious approach to "risk-based" decisionmaking about the non-clinical and clinical program may thus be warranted for early biosimilar mAb products. Finally, we agree with the recommendation that biosimilar applicants use homogeneous populations during clinical testing, because this approach reduces variability and, correspondingly, the sample size	A general sentence has been added. However, whilst BMWP agrees in principle with the comments made, this is not restricted to biosimilar mAbs but the general biosimilar philosophy. Any Applicant is expected to follow closely also the general biosimilar guidelines where the principles are explained. As explained in the guideline, a toxicology study in a relevant species may not always be possible. Applicants, when having less experience, would then use the route of scientific advice

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	needed to exclude differences. Tests in homogeneous populations, however, may not reveal important differences between the reference product and the proposed biosimilar that manifest only in patient subpopulations (e.g., immune-compromised patients and patients with previous exposure to a therapeutic biologic). In most cases, therefore, it will be necessary to supplement testing in homogenous populations with broader testing and/or testing in special subpopulations. In any case, biosimilar applicants should always justify the populations used during clinical development and clearly indicate in the summary of product characteristics (SPC) which populations were studied and which were not.	with a concept based on interim data when determining levels of risk. Again, the concept of biosimilarity is not to bypass testing and to get an as easy programme as possible, but to generate comparative data in meaningful and tailored studies. Justification of the clinical models chosen is a prerequisite. Testing in subpopulations may not be warranted, and it is not clear if the request for tests based on 'important differences that manifest only in patient subpopulations' is based on data or theoretical.

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		The principles of what information will be put to the SmPC are still to be determined and are beyond the scope of a scientific guideline. The SmPC will be up to the CHMP to decide for an individual biosimilar mAb.
6	• Although a case-by-case approach in guidance is principally appreciated, the lack of detail in the current guideline (especially on non-clinical and clinical requirements for biosimilar mAbs) and the frequent invitation to make use of the scientific advice procedure does not translate into transparent regulatory requirements for approval.	The guideline is meant to introduce general principles for biosimilar mAbs. At the present stage, it is not appropriate to issue product-specific guidance, since more experience yet has to be gathered. Therefore, the BMWP considers that the level of detail in the guideline is appropriate for the current stage of knowledge and experience.
	• The EMA could consider to re-structure the document to provide separate sections for different indications and/or different disease states to circumvent being too vague in guidance. Alternatively, indication specific guidelines could be considered to fill the gaps. • Labelling of biosimilar mAbs: data source must make clear and transparent which data (safety and efficacy) were obtained via extrapolation and which data reflect those of the originator product and those of the biosimilar, respectively. • Biosimilar mAbs should either have a unique INN and/or a separate brand name; prescriptions should be made by brand	Please see comment above. It is too premature to go for indication-specific recommendations. The information that will be put to the SmPC will be up to CHMP and is not part of a scientific guideline laying down the requirements for a biosimilar mAb development.

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	name allowing unambiguous traceability to the patient level. • A switch from the original to a biosimilar mAb should only be made with the express consent of a physician (no automatic substitution at the pharmacy). This is in line with an express recommendation of the EMA (EMEA/74562/2006).	INN and naming is beyond the responsibility of the BMWP and therefore not subject to this guideline. Switching, substitution, and interchangeability are a national decision and beyond the scope of this guideline.
7	The BioIndustry Association (BIA) supports the overall spirit of the European Medicines Agency draft guideline on similar biological medicinal products containing monoclonal antibodies. In general, the guideline is science-based and useful, providing guidance to those planning to develop biosimilar versions of existing originator monoclonal antibodies. The guideline attempts to cover a very wide and diverse group of products, including some novel types of monoclonal antibodies not yet envisaged as potential biosimilars. For this reason it has to allow for a range of circumstance and be potentially very flexible. However, this partly limits its usefulness and may leave sponsors requiring further specific scientific advice from regulatory authorities. It may be more appropriate to revisit the concept of having sub-class specific sections/appendices or providing additional details rather than referring to a case-by-case approach. Such an approach will also have to gain support from individual EU Member States reviewing clinical	Regarding the need for toxicology studies please see previous comment. In principle agreed that indication- or product-specific guidance would be useful than a case-by-case approach. However, although numerous scientific advices have been

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	trial authorisation applications on the basis of reduced data. The guideline does not address if an overall minimum data standard is acceptable. Since flexibility is offered in a number of areas, the guideline does not address whether a minimal approach across all aspects of non-clinical and clinical evaluation would meet the agency's tolerance to allow abbreviated study. There is a need for clarification on the expected standards, as there is potential for misinterpretation.	given, there has not been a single marketing authorisation assessment yet at the time the guideline was written. Therefore, it is considered too premature to give more specific guidance. It is virtually impossible to define a "minimum data standard". For example, for a biosimilar mAb expressed in a common expression system the analytical requirements would probably be different as compared to one expressed in an expression system where limited experience exists. Therefore, definition of a "minimum data standard", although in principle desirable, could be counterproductive.
	The guideline could be interpreted that *in vivo* non-clinical studies should not be routinely applied to biosimilar products prior to dosing in man. We agree that large scale comparative studies are unlikely to be valuable. However, due to the lack of ability to fully characterize the physico-chemical properties of the biosimilar and incomplete understanding of the mechanisms of off-target toxicity of biological therapeutics, we recommend that all biosimilars undertake a limited repeat dose *in vivo* study in a pharmacologically relevant species prior to human dosing. With regard to extrapolation of indications, the guideline presents an alternative approach that requires further discussion. The BIA welcomes the opportunity to submit these observations and	The guidance aims at helping Applicants to design a tailored development programme with the aim to establish biosimilarity rather than with the aim to have an easy and abbreviated study programme. Please see non-clinical part of this document.

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	comments and take part in the planned workshop on this topic. We hope our comments are helpful in improving this guideline with greater clarity.	
8	Our learnt Society, in the last few years, has scrutinized carefully the effectiveness of the first specific guidelines on biosimilars issued (ie EPO and GCSF) in delivering safe and effective products. In this setting, we acknowledge the effectiveness of the guidelines so far issued. In this context, we therefore feel that the guidelines on monoclonal antibodies are in the most part appropriate in the context of safe-guarding efficacy and safety of the medicinal product. Our overall opinion of these guidelines is therefore very positive. The comments contained in this document therefore attempt to clarify some issues that might be read as distinct in principle from the original EMA positions on comparability.	
9	1. Recommend EMA cite its existing BE guidance noting exceptions (if any) that do not apply to biosimilars. 2. Cite WHO guidance about acceptability of non-inferiority to support a biosimilarity claim and ask if EMA agrees. 3. The guidance may suggest to consider use of stratification by tumor burden or receptor shedding to insure baseline comparability. 4. The guidance may clarify more stringent evaluation criteria for showing similarity in non-clinical comparability studies to exclude	The bioequivalence guideline is cited, but exceptions not explicitly mentioned, since the approach should be kept flexible. WHO guideline not cited, since non-inferiority would be an exception (please see relevant wording in final guideline text). Proposal put to guideline.

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	all differences of importance in the concentration. 5. The guidance may comment on the use PD marker (if there exits) to provide evidence for biosimilarity. For a mAb product, if there exits a PD marker which is mechanistically linked to its pharmacodynamics, comparability documented on this level in the different indications can provide evidence for biosimilarity independent of the fact that not in all indications the PD marker translates directly into clinical benefit. It is the biosimilarity concept to deduce the requirement of clinical studies for MA based on evidence of similarity provided at several levels, of which PD is one. 6. During the EMA workshop on biosimilar monoclonal antibodies on July 2nd, 2009, the use of Bayesian statistics was proposed to "help optimize clinical trial sample size" (mAbs (2009) 1: 403). If EMA agrees with this position, it should be included in the draft guidance. Reference: Reichert JM and Beck A (2009) mAbs 1, 394-416	BMWP considers that this aspect is sufficiently covered by the current text. The methodology to be applied is up to the Applicant. BMWP considers that a recommendation for Bayesian statistics would at the present stage go to far, since no experience has yet been gained. However, Applicants can certainly use such methodology, at their discretion.

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10	Comment: The existing EMA biosimilar guidelines are very narrow in therapeutic focus/product specific (e.g. biosimilar guidance's for Erythropoietins, low-molecular-weight-heparins etc). The guideline for monoclonal antibodies (mAb) is very broad covering a range of indications for mAbs. Elan suggests that it may be more appropriate to develop several mAb biosimilar guidelines based on the therapeutic indication or broader therapeutic area (e.g. one guideline for mAbs in cancer, one for immunological mAbs etc). More specific narrowly defined mAb biosimilar guidelines would be more useful and reduce uncertainty. Proposed change (if any): Develop multiple, more narrowly defined mAb biosimilar guidelines. Comment: Elan does not recommend under any circumstances that automatic substitution or interchangability be allowed due to the fact that the biosimilar mAb will not be "identical" to the reference product. Mere comparability by EU guideline is in our opinion not enough for automatic substitution or interchangability. • Interchangeability and substitution are currently under the strict responsibility and decision of the EU member states. Because of the complex nature of mAbs and the fact that mere comparability by EU guideline is in our opinion not enough for automatic substitution or interchangeability, Elan recommends introducing in the guidance a	Please see answer to similar comments above. Please see answer to similar comments above (this is outside scope of the guideline).

[1] EMA, Omnitrope: EPAR - Scientific Discussion, 2006. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500043692.pdf>
[2] EMA, Valtropin: EPAR - Scientific Discussion, 2007. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000602/WC500047158.pdf>

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	position on interchangeability and substitution. • Interchangeability can present a risk to patients. It is important to maintain treatment equilibrium at patient level. The first aspect to consider is the level of similarity. The scientific and technical comparisons that are being made between a biosimilar product and a reference product are critical. The reference mAb, as well as the level of data available and market experience for the reference mAb, are important elements to take into account when talking about interchangeability and substitution. • Another aspect is what can be justified theoretically (e.g. existing	Please see answer to similar comments above (this is outside scope of the guideline).

[3] EMA, Binocrit: EPAR - Scientific Discussion, 2007. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000725/WC500053615.pdf>
[4] EMA, Valtropin: EPAR - Scientific Discussion, 2007. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000726/WC500028287.pdf>
[5] Abseamed: EPAR – Scientific Discussion, 2007. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000727/WC500020666.pdf>
[6] EMA, Silapo: EPAR – Scientific Discussion, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000760/WC500050914.pdf>
[7] EMA, Retacrit: EPAR – Scientific Discussion, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000872/WC500054374.pdf>
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[9] EMA, Tevagrastim: EPAR – Public assessment report, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000827/WC500036667.pdf>
[10] EMA, Biograstim: EPAR – Public assessment report, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000826/WC500053904.pdf>
[11] EMA, Filgrastim ratiopharm: EPAR – Public assessment report, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000824/WC500022727.pdf>
[12] EMA, Zarzio: EPAR – Public assessment report, 2009. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000917/WC500046528.pdf>
[13] EMA, Filgrastim Hexal: EPAR – Public assessment report, 2009. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000918/WC500022471.pdf
[14] EMA, Refusal assessment report for Alpheon, Procedure No. EMEA/H/C/000585, 2006. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000585/WC500070792.pdf>
[15] EMA, Questions and answers on the withdrawal of the marketing authorisation application for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel, 2008. Available at <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500067088.pdf>

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	data) and what can be demonstrated with additional data. The traditional model of developing a biosimilar, involves full quality development and comparison with the reference product, and reduced data packages for non-clinical and clinical. Similarity must be established at each stage against the reference product. Due to the reduced non-clinical and clinical data packages, analytical differences are crucial in the justification necessary to conclude that a product is truly "biosimilar".	Please see answer to similar comments before (this is outside scope of the guideline).
	• In Nature Biotechnology Schneider and Kalinka state: "Monoclonal antibodies…are considerably more complex than currently developed biosimilars, such as human growth hormone, insulin or erythropoietin. It is entirely possible that, compared with a brand product, biosimilar monoclonal antibodies may display subtle differences in molecular structure that can not be detected by current methods. It will likely be challenging to demonstrate that such differences have no adverse impact on clinical efficacy and safety…Indeed, glycosylation patterns are likely to be among the most crucial issues for the development biosimilar monoclonal antibodies, because these modifications can influence binding, immunogenicity and effector activity of a monoclonal antibody molecule." (Source: C. Schneider & U. Kalinka (2008) Nature Biotechnol. 26, 985-990).	BMWP considers that this aspect is sufficiently covered also when read in conjunction with the general biosimilar guidelines.
	• The guiding principles for innovator and biosimilar companies should be the same. The case by case approach, as expressed in the European legislation and the notion of "class of biosimilar" are critical when developing guidance for mAbs and the current background experience demonstrates the complexity of this class of product. Elan therefore believes it is inappropriate to draw long-	Quality aspects will be discussed in the revised general quality guideline on biosimilars.

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	term conclusions on substitution and interchangeability. • Another element is the importance of clinical data and the design of the studies to demonstrate efficacy and safety similarity. A similar efficacy does not necessarily imply a similar safety profile and sufficient clinical data are required in a sufficient number of patients in order to establish the initial safety profile before authorisation. Proposed change (if any): Due to the fact that a biosimilar mAb will not be "identical" to the reference product, automatic substitution or interchangeability should not be allowed under any circumstances. Comment: The guidelines are well defined and cover the major aspects of mAbs. The draft guideline concentrates on non-clinical and clinical issues, and based on the particular nature of mAbs, the development of specific quality guidance for biosimilar or second-generation mAbs is justified. However, Elan would like to recommend the following: 1. Take into consideration the technical amendment to Directive 2001/83/EC introduced by Commission Directive 2003/63/EC of 25 June 2003. As this technical amendment outlines the framework for similar biological medicinal products it is particularly relevant to mAbs. 2. As to the clinical aspects, the following points are recommended: • PD markers cannot be considered as surrogates of similarity. Because of the nature of mAbs, clinical studies to establish a claim of similarity in terms of efficacy and safety should be the same as for the	See answer to similar comments before (outside scope of the guideline). BMWP agrees but considers that this aspect is sufficiently

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	reference product, at least as far as the pivotal study is concerned. Comment: The introduction to the guidelines (lines 93 and 94) states correctly that it may be difficult to conclude the relevance of minor quality differences in the physiological and biological characterisation of such products, and refers to existing guidelines such as the quality guidelines for biosimilar products (EMEA/CHMP/ 49348/05) and the guidelines for mAbs (CHMP/BWP/157653/07). Elan recommends that a separate document for quality be developed for mAbs, rather than amending the current quality guidelines for biosimilar medicinal products (EMEA/CHMP/49348/05) as stated in the concept paper (EMA/CHMP/BWP/617111/2010). We believe that in light of the accumulated experience it is relevant to amend document EMEA/CHMP/49348/05 for biosimilar medicinal products, but a separate quality guideline for biosimilar mAbs is justified because of the following reasons: • The 3 dimensional data set that innovator companies generate though standard process development and comparability is unique and allows the company to maintain the right level of control on the specificity of the product. This data set is not available to biosimilar companies because they benefit from the concept of "accelerated development" with a full quality package but limited non-clinical and clinical data. The paradigm "the process is the product" is a valid statement for	covered. Please see answer to similar comments above (outside scope of the guideline).

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	biosimilars and particularly relevant for antibodies as it translates that under the current state of scientific knowledge two protein products manufactured out of two different processes will unlikely have strictly identical properties. Due to the limited development history by the biosimilar company historical data will not be available to justify the differences that may have an impact on the benefit risk profile. A specific quality guidance for biosimilar mAbs could establish the minimum principle required in order to conclude comparability with the reference product and allow to test the product in clinical trials.	
	• The European biosimilar regulatory pathway has been tested for more than 5 years, with the concept of '*accelerated development*'. An innovator product will always undergo a complete development program. For a biosimilar medicine, the complexity of the molecule requires generating a minimum level of clinical data. However, European regulatory authorities generally accept that a biosimilar manufacturer will not conduct the same number of studies as reported in the initial filing package of the originator product. By contrast, this concept of '*accelerated development*' where less data are generated requires a manufacturer to be extremely accurate on the quality development and validation, and more cautious with the safety profile of the product in the initial phase of marketing and later. This is specifically relevant for monoclonal antibodies and justifies a separate guidance for biosimilar or second-generation mAbs. This is even more relevant when analysing the current experience with other classes of biosimilar for which the impact of quality issues can	BMWP does not agree. As explained in the guideline document and in the general biosimilar guidelines, the clinical trial design for a new medicinal product aims at establishing benefit, while the aim of a biosimilar development is to establish biosimilarity. Therefore, trial design including endpoints will inherently be different. BMWP does not agree. The principles for establishing acceptable quality are not different to new mAbs, and therefore as regards methodological considerations the guideline on quality requirements for mAbs applies. As regards comparative considerations, the principles as stated in the general quality guideline on biosimilars, especially when revised, should suffice.

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	perhaps be considered less significant than those of mAbs. The submissions made to the EMA allows understanding the approach and the limitations of the concept of '*accelerated development*', as well as the way biosimilar manufacturers may interpret it. In general one can argue that three classes of products for (at the time of this analysis) a total of thirteen products have been approved in the EU, i.e. somatropin (rhGH)[1] [2], Epoetin (rhEPO alfa[3] [4] [5] and zeta[6] [7]), and filgrastim (G-CSF[8] [9] [10] [11] [12] [13]). Two other classes of products, the applications of which were submitted to the Agency, did not meet the requirements for similar biological products, i.e. interferon alfa (CHMP refusal), and insulin and interferon beta (application withdrawn). In these above-mentioned cases, the CHMP could not conclude on the comparability of the applicant products versus the reference products because of deficiencies identified in the areas of Quality, Safety, and Efficacy[14] [15]. It seems that the current guidance may not be sufficient to cover the requirement for mAb because of the notion of similarity against a reference product. The general quality guidance on mAbs may not be relevant because it doesn't take into account similarity with a reference product. • The guidance for mAbs was last revised in 2007. However the previous version was revised in 1994 and the guidelines were into effect in 1995. So, this guidance is not developed for comparability purposes but for the development of mAbs in general terms. The proposal for specific Quality guidelines on biosimilar mAbs or second-generation mAb should be able to address this issue.	The company developing a biosimilar will generate an own head-to-head dataset as regards molecular characterisation which forms the basis of the biosimilarity exercise. Since critical quality attributes and other parameters may differ between different mAb reference products, it is virtually impossible to define minimum principles in a guideline. Likewise, defining minimum principles could result in the misunderstanding that fulfilling these would already be sufficient for a biosimilar mAb. This could result in lower quality dossiers. BMWP considers that a thorough comparability exercise on the quality level together with the non-clinical and clinical data generated head-to-head will establish that minor differences, should they occur, will be acceptable at the time of marketing authorisation application.

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	Proposed change (if any): Based on the particular nature of mAbs, the quality aspects of mAbs merit attention and developing separate and specific quality guidance for biosimilar or second-generation mAbs seems to be the way forward.	See above. A comparison on a quality level with state-of-the-art methodology is a prerequisite of a biosimilarity development programme.
11	In concept, we agree with the hierarchical, risk-based approach to evaluate mAbs on a case-by-case basis to help determine the choice and extent of *in vitro* and *in vivo* non-clinical studies. However, we are concerned that the draft guidance does not provide sufficient directions for decision making on the extent of non-clinical studies or guidance on acceptance of variance between a biosimilar product and reference product. Additional definitions and more specific criteria for acceptable variance in comparability studies are needed in the guidance to clarify its requirements. We also are in agreement with the recommendation to focus on *in vivo* non-clinical aspects of comparative pharmacokinetics (PK) and pharmacodynamics (PD), based on the need for additional information, and not on large comparative toxicological studies in non-human primates. With respect to the clinical development, we concur with the concept that a comparative pharmacokinetic study in a sufficiently sensitive	The class of mAbs is in the view of BMWP too diverse as to allow for definition of more specific criteria. It is the totality of data, based on a thorough comparability exercise on a physicochemical and biological characterisation that founds the basis for accepting a biosimilar. The non-clinical part is revised to reflect major comments made. Nevertheless, to define more specific criteria in absence of data so far and also considering the vast differences between different reference products (mechanism of action, target specificity etc.) it is not feasible to define more specific criteria.

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	and homogeneous study population is an integral part of biosimilar development. We agree that dose/concentration-response relationships provide strong evidence of biosimilarity, and that the focus in these settings is demonstrating not patient benefit, but similarity to innovator, for which patient benefit has already been established. We also concur that PK data will be helpful for extrapolation to other indications not specifically studied in clinical efficacy studies, based on scientific justification and rationale. In addition to the specific questions/clarifications highlighted below, we ask the agency to consider including a decision tree to add more clarifications and consistencies for following the hierarchical approach; i.e. condition criteria and decision points for when and which *in vivo* studies should be considered. We also suggest including specific guidance regarding the use of reference materials (e.g., origin of materials for *in vitro* and non-clinical studies as well as clinical studies; minimal number of batches to be characterized, especially for *in vitro* studies) in establishing biosimilarity.	Please see comments above. Use of reference materials etc. is an important aspect, but is beyond the scope of a scientific guideline (it would be important for the entire "class" of biosimilars). Requirements may also be different in various member states.
12	1. How do you define the promise of Biosimilars for the treatment of a chronic lifelong disease with a high prevalence, such as psoriasis? • More competition leading to lower prices. However, equal	BMWP would like to thank this stakeholder for the survey that was performed. This is very helpful. However, it appears that at least some participants in the survey have not entirely understood the way biosimilars are developed: A biosimilar development programme is focussed on establishing

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	efficacy and safety data should be provided by biosimilars. • To reduce costs for the management of these diseases and still provide the high efficacy seen under biologics. • The main objective of biosimilars should be promoting the accessibility of patients to such therapies through the substantial reduction of the total economic cost of treatment. • The complexity of the molecules and the need for more stringent definitions of equivalence impacts the promise of biosimilars. 2. When prescribing a biosimilar agent you must have data to support therapeutic equivalence versus bioequivalence (agree / disagree) • 100% of respondents answered Agree. 3. What minimal data will you look for in order to support prescribing a biosimilar therapy? a) Pharmacokinetic, efficacy and safety data from animal models b) Pharmacokinetic comparisons in small human trials (10 - 20 patients) c) Effectiveness (non-statistical), Safety and Pharmacokinetic information in relatively small human trials (40-50 patients) d) Efficacy (statistically supported), Safety and Pharmacokinetic information in larger human trials (>200 patients) • 100% of respondents selected answer d) Efficacy (statistically supported), Safety and Pharmacokinetic information in larger human trials (>200	biosimilarity, not clinical benefit (which has been established already before by the originator). This consideration drives the design of clinical studies, and also considerations around extrapolation. It should be noted that pricing is outside the remits of the BMWP, but one could speculate that higher requirements (post-authorisation follow-up, mandatory registries as requested here, clinical studies in all indications etc.) would have an impact on the price of a biosimilar – one needs to find a balance, otherwise biosimilar development becomes unfeasible. Interchangeability etc. is outside the scope of this guideline, as explained elsewhere in this document.

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	patients). Comments: • As can be seen in the epoietin experience, one needs to FULLY characterize each compound produced as a "biologic." • Best would be a RCT head-to-head with the parent compound. • The equivalence margins are far too small to yield anything more than slightly biosimilar. 4. Do different biosimilar therapies have to be easily distinguished from other biosimilar agents and innovator products (Yes / No). Why? • 100% of respondents answered "Yes" Comments: • Small modifications may lead to different side-effects, safety profile etc –there has to be a mechanism to monitor such differences in practice • Each biosimilar should be regarded as a clearly separate compound (more dissimilar than conventional chemical drugs). • Although they may gain the category of biosimlars, they are in effect different drugs. • Many issues can arise. For example, what if one biosimilar induces antibody formation that affects the original drug or other biosimilars? 5. What aspects of biosimilars need to be different from the original innovator agent to support identification of the specific therapy; please	

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	prioritize (1 = most important, 4 = least important) a) Brand / Proprietary name b) Generic / Non-proprietary name c) Packaging (Colors) d) Classification • 60% of respondents answered a) Brand / Proprietary name and b) generic / non-proprietary name as the most important mechanisms to distinguish biosimilar agents 6. Is it important for a physician to know that a patient is receiving a biosimilar agent versus an innovator agent (Yes / no) Why? • 100% of respondents answered "Yes" Comments: • Until proven different, a biosimilar is a "novel" drug. • Any physician is responsible for the prescription. A prescription is not just a brand name, but a recommendation based on a guaranteed quality of the product prescribed. • To be alert in case of unsuspected efficacy or safety issues. • To better judge treatment outcomes and safety assessments. • Clinical differences may appear on long term basis. 7. What mechanisms might be introduced to combat interchangeability (the switching of a patient to a biosimilar at the pharmacy, mandated by hospital policy or payors) Comments:	

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	• The physician needs to prescribe EXACTLY which drug he/she wants the patient to receive. If necessary, one might have to specifically state that the pharmacy MUST NOT change the prescription. • EMEA and FDA mandated requirement for adhering to "dispense as written" instructions from the prescriber • Biosimilars, because of their characteristics, may be considered a different category of non- interchangeable "drugs" • There must be the ability to require DAW • Sound data background. If the new compounds are indeed similar in all aspects I don't know of any reason not to use them • Biosimilar versus bioequivalence. The issues are: what are the true differences in efficacy? What are the short and long term prospects of antibody production? What cross-reactivity is ascertained between antibodies to biosimilar and innovator brand? 8. What is the best way to monitor patients on biosimilars with a view to collecting data to support biosimilar use and to minimize any risks or uncertainties? Comments: • Mandatory 5-year safety follow-up. • Registries should be required to include biosimilars and all treatments for psoriasis.	

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	• Post marketing vigilance. Implement national vigilance programs, possibly centralized by Dermatology Societies such as the international Psoriasis Council. 9. Should a biosimilar agent receive total class labeling for all indications based upon one study in a single indication? For example, should clinical studies for a TNF-inhibiting biosimilar performed in rheumatoid arthritis be also sufficient for an indication for psoriasis. (Yes / no) Why or why not? • 70% of respondents answered "No"; 30% of respondents answered "Yes" Comments: • We see differences between biologics with similar modes of action between indications. Thus, some variability may be expected, which might affects the rationale to use a biosimilar in different indications • Biosimilars should have to be proven effective for every indication, just as innovator biologics. The size and complexity of this sampling may be different (and cheaper to perform) but they would have to be proven effective and safe in humans for individual indications. • Higher doses are often required in psoriasis. Monotherapy is the rule in psoriasis, while combination therapy is standard in rheumatoid arthritis. In this context it should also be noted that methotrexate changes the pharmacokinetics of some TNF-inhibitors. • Different diseases need different clinical and pharmacologic	

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	studies. • There are differences in the pk-pd models for the innovative products. The margin of biosimilarity is far too coarse to derive reliable estimates of response across indications. 10. What other thoughts do you have related to Biosimilars? (e.g. related to therapeutic rationale for their use; or maintaining the physician-patient continuum of care?) Comments: • We need to decrease the cost of biologics and allow access to these wonderful medications for a greater number of patients. • My major concern is essentially related to the commitment to regulating biosimilars to ensure good efficacy, tolerance and safety. • Pricing is a concern. Unless prices really do decrease significantly, why do we need biosimilars? • It might turn out that a proposed biosimilar in clinical assessment shows superior efficacy compared to the original. This may be due to different pharmacokinetic properties. Would this mean that the biosimilar become a second generation biological? • Key is really to show immunological similarity! • Biosimilars have to show the same characteristics of originals in all aspects of the issue, with better accessibility and lower prices.	

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	• Manufacturing stringency has to be maintained and regulated given the delicate manufacturing processes.	
13	This guidance (Guideline on similar biological medicinal products containing monoclonal antibodies) is surely an important step forward with regard to facilitating patent access to safe and effective but also less costly medicinal products. I further think that in relation to already existing product specific guidance documents, this new guidance document is the most progressive due to its wider scope and forward viewing emphasis for example with regard to the introduction of the concept of Extrapolation of indication for a Biosimilar The explicit mentioning of and encouraged usage of "Meta Analysis" in this guide However as in any progressive document, there are few areas which require further clarification. Although these areas are not specifically linked to mAbs and moreover to Biosimilars in a more general way, this guide uses some key terminology and concepts such as: 1. Extrapolation of Indications 2. Meta Analysis 3. Conventional Equivalence Margin , which require further explanation. I feel it would be appropriate either to clarify those terms and concepts as part of this guide or to address them in a separate guide, applicable for all Biosimilars taking into account the heterogeneity and the nature of mAbs (and other Biosimilars).	

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	The EMA guide EMEA/CHMP/BWP/49348/2005 and subdivides variability in: i) Product variability ii) Process related variability. Those two variability types form what is called the "Quality Profile" of the Biosimilar. However these types of variability are relevant for all biotechnological derived medicinal products, be it the Reference Medicinal Product or be it the Biosimilar. One particular issue is in my opinion the variability of the Reference Medicinal Product itself. 1.) Therefore the variability of the Reference Medicinal Product itself (as a variable) leads to questions on how to fulfil requirements for the Biosimilar i.e. to demonstrate comparable clinical efficacy and safety versus the Reference Medicinal Product. Or differently expressed: 2.) When requiring any direct comparison, be it in a non-clinical or clinical setting, batch to batch variation of the Reference Medicinal Product (due to the glycosylation heterogeneity of mAbs or process impurities associated with the production of mAbs i.e. the full quality profile of the Reference Medicinal Product) and the quality profile of the Biosimilar need to be taken into account when designing studies and analyzing data. I call this train of thoughts in this submission the "overlaying issue of	The "overarching" guideline and the general non-clinical/clinical guideline are subject to revision. However, the BMWP feels that terms like "conventional equivalence margin" do not require further explanation, since they are either defined in other CHMP guidance being referred to by this guidance, or where an explanation is given (e.g. in the mAbs guidance: "widening of the conventional equivalence margin beyond 80-125% requires thorough justification", where 80-125% is the definition of "conventional"). The "quality profile" is these two sorts of variability PLUS the usual stand-alone physicochemical and biological characterisation PLUS a comprehensive comparability exercise. As such, the "quality programme" for a biosimilar is more extensive than that of a stand-alone.

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	product heterogeneity and variation [(1)]". This "overlaying issue of product heterogeneity and variation [(1)]" is founded on and also (partially) reflected in the following documents: *1.) "Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues".* *Section 3 (Problem statement)* Which takes into account the life cycle of the Biosimilar and variations of the process, impacting the variability (Quality Profile) of the Biosimilar. This is of relevance for any Biological Medicinal Product, be it a Reference Medicinal Product or Biosimilar. This "overlaying issue of product heterogeneity and variation [(1)]", appears also to be justified taken into account the exiting guidance: *2.) Doc. Ref. EMEA/CHMP/BMWP/101695/2006* *GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS NON-CLINICAL AND CLINICAL ISSUES* *"Demonstration of comparability is a sequential process, beginning with quality studies (limited or comprehensive) and supported, as necessary, by non-clinical and/or clinical studies.* *This guideline will address the requirements for non-clinical and/or clinical bridging studies to demonstrate that the modification has no impact on safety and efficacy.* *The selection of non-clinical versus clinical testing is product-driven, i.e. a model should be chosen that best detect clinically relevant*	

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	differences with sufficient accuracy" *3.) Doc Ref: EMEA/CHMP/BWP/49348/2005* *GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES* *"Consequently, an extensive comparability exercise will be required to demonstrate that the biosimilar and reference products have similar profiles in terms of quality, safety and efficacy.* *Based on the comparability approach and when supported by sufficiently sensitive analytical systems, the demonstration of comparability at the quality level may connect the biosimilar product to the nonclinical and clinical data previously generated with the reference product" "It is recognised that each medicinal product is defined by the molecular composition of the active substance resulting from its process, which may introduce its own process related impurities. Consequently, the biosimilar product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/impurities), and ii) related to its process"* *4.) CHMP/437/04* *GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS* *"Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products*	

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	(recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). *Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be 'minor' in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.* *Therefore:* – The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived medicinal products. Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products. The " similar biological medicinal products" approach, based on a comparability exercise, will then have to be followed"	
14	Novartis would like to thank the European Medicines Agency for the well-considered draft guideline on biosimilar monoclonal antibodies. We are especially content with the science-based approach of the guideline that a) bases the proof of similarity between biosimilar and reference product on the physicochemical and biological analysis as the prerequisite to justify targeted preclinical and clinical biosimilar development; b) allows for regulatory case-by-case decisions where indicated; and c) recognizes the principle that the basis of the biosimilarity exercise is to demonstrate the product's similarity to an already approved medicine with regards to quality, safety and efficacy rather than to demonstrate independent patient benefit per se.	

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	We consider the case-by-case approach as suggested in the guideline essential for the regulation of all biologics (biosimilars and originator products alike) in order to accommodate product- and class-specific characteristics. Both, the comparability exercise that assesses potential differences in quality attributes of biologics upon manufacturing changes and the biosimilarity exercise a) are led by a decision tree where each step is informed by the results of the previous one; b) make reference to the safety and efficacy established for "another" product; c) rely on the demonstration of high physicochemical and biological similarity which informs further preclinical/clinical assessment to ensure that observed differences do not negatively impact safety and efficacy. In the context of biosimilar monoclonal antibodies, we consider this guideline overall appropriate and helpful in providing clarity about the comparability exercise. We would like to draw your attention to recent publications that further explain the rationale of our approach (Nature Biotechnology 29, 310-313, 2011 and mAbs 3:2, 209-217, March/April 2011). In those cases where comparability would not suffice, available guidance for the respective clinical conditions should be further consulted. We appreciate the guideline as a major step to help increase patient access to high-quality medicines in the EU that can serve as well as a guiding principle for other regions of the world.	
15	We broadly support both the overall spirit and the large majority of the specific recommendations made in the draft guidance. The guidance is highly scientific and appropriately permits the application of scientifically-driven judgement to individual products and situations. However, the guidance could be made even more useful for	

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	developers of this class of products if the specific comments provided in the following sections of these comments were to be incorporated into the final guidance. Given the complexity of the issues raised by this product class, we also suggest that a public workshop on the topic would be valuable. In addition, the term equivalence is used multiple times throughout the draft document; this may be confusing to some readers since it is not expected for these products to be equivalent.	BMWP acknowledged the need for a workshop, which was therefore organized and held in October 2011. "Equivalence" is normally expected for a biosimilar as compared to its reference medicinal product.
16	In general, Synthon welcomes the current draft guideline and acknowledges it is a very comprehensive and well written document. However, the current draft guideline does not provide a recommendation for the statistical design of equivalence studies, and no specific guideline is (yet) available. According to the guideline on bioequivalence studies for generic products (CPMP/EWP/QWP/1401/98), a statistical design with a 90% confidence interval is recommended and well accepted to test equivalence of the test and reference products in terms of bioavailability. As this is the only guideline currently available that provides recommendations on the statistical design of studies aimed to demonstrate equivalence, the same may apply for the equivalence studies discussed in the current draft guideline. Consequently, a phase III study for a similar	BMWP considers that it is currently premature to give more detailed guidance as regards statistical recommendations, also given the wide variability of clinical efficacy, patient populations, endpoints, clinical conditions etc. in which the class of mAbs would be studied.

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	monoclonal antibody may be designed to show equivalence using a 90% confidence interval.	
17	*General introductory comments* EGA would like to applaud the EMA and CHMP for this excellent, very comprehensive and very well written document. There are many very positive statements included which underpin the leading role of the European regulators in establishing science based approaches for the development of biosimilar products, including more complex biosimilar products. A few examples to mention: • Clear statement of biosimilarity exercise: ´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´ • The guideline suggests short and lean clinical development, e.g. comparative PD study alone could be sufficient (under certain circumstances) instead of full efficacy study along with sufficient safety data. See under 5.3. where it is mentioned ´Clinical efficacy phase III studies are only required if biosimilarity can not be demonstrated in valid PK and PD (including dose-concentration-response relationship) studies!´ • Also the fact that shorter evaluation time points and/or alternative endpoints may be acceptable is very positive, e.g. ´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	

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	gathered in a post-authorisation setting, where feasible and considered necessary.´ *Nonclinical* We highly appreciate the proposed approach for the nonclinical evaluation of mAbs as outlined in this draft guideline. Allowing for a scientifically based case-by-case evaluation whether or not nonclinical studies have to be performed is a major step towards reducing unnecessary animal testing. We also would like to draw your attention to the specific comment to line 125, please see below. *Clinical* The development strategy for biosimilar products is to assess biosimilarity as a stepwise approach. This should also apply to the development of biosimilar mAbs and accordingly it is deemed justified to continue with an abbreviated non-clinical and clinical study program, once biosimilarity between the biosimilar and the reference product has been demonstrated on the basis of a rigorous comparability exercise with regards to the physico-chemical and biological properties. It is assumed that in-vitro biological assays do not reveal any differences between the biosimilar and the reference product prior to moving into in-vivo studies. Therefore, it is surprising to see the request to first perform human PK testing before moving into Phase III trials as outlined in the mAbs guideline. It is argued that it was unethical to move ahead with Phase III trials if there was a difference in human PK. However, even if human PK data observed slight differences in PK behaviour, this could still be acceptable if Phase III	

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	data demonstrated no impact on safety and/or efficacy. Therefore, we believe that there should not be such a categorical request for sequential testing but rather a case-by-case assessment based on the data generated for the mAbs. We would appreciate if it could be clarified more clearly that for some diseases, such as oncology, non-inferiority designed trials for efficacy are justified and fully acceptable in order to reduce the number of patients for Phase III trials and thus accelerate market access of biosimilar products. *General comments regarding the terminology 'anticancer' and 'cytotoxic'* According to our opinion, the antibody-based targeted therapies have sharp difference both in the mechanism of action and adverse event profile compared to classical cytotoxic drugs. On the other hand, investigating cytotoxic drugs in healthy volunteers (Phase I trials, e.g. comparative PK) might raise serious ethical concerns. However, the words „anticancer" and „cytotoxic" are used as synonyms several times in the draft guide: *line 282: "Pharmacokinetics of anticancer (cytotoxic) mAbs may be*	Line 260 of the draft guideline states that "usually" PK studies precede clinical trials. This implies that deviations are possible, and BMWP considers that this is not a categorical request but rather represents the often employed "stepwise approach" to developing a biosimilar. As such, it may be wise to first study PK profiles to have a clearer picture if the biosimilar candidate is "similar enough", especially in cases where in-vitro biological assays are not sensitive or too variable. Again, the strategy depends on the case and is therefore up to individual decisions. A stepwise approach, where possible, may "de-risk" a biosimilar development programme if differences were observed before commencing a large clinical trial.

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	time dependent" *line 433: "If a reference mAb is licensed both as an immunomodulator and as an anticancer (cytotoxic) antibody"* In addition, in the draft guide monoclonal antibodies are indicated as cytotoxic agents: *line 27: "Additional considerations for PK measurements of cytotoxic mAbs in anticancer"* *line 85: "Different mAb products share some properties, e.g. being cytotoxic to their target"* *line 245: "In such case (e.g. many cytotoxic mAbs with cellular targets)"* Based on the scientific literature, clearly the terms "cytotoxic" and "anticancer antibody" are not synonyms. We deem that anticancer monoclonal antibody drugs are not cytotoxic agents by themselves. The scientific basis to support this opinion is highlighted as follows. Usually, a drug is regarded as cytotoxic if the drug can kill the target cells (by necrosis and/or by apoptosis) effectively. In general, the maximal effect of an anti-cancer monoclonal antibody is far from being able to reach the IC50 (half maximal inhibitory concentration in case the investigated biological response is cell death) *in vitro*. In contrast, dose-response curves of cytotoxic anticancer drugs (anthracyclines, taxanes, vincas, etc.) can reach the IC50 easily. A higher cytotoxic effect (including even IC50 as a measure) can be reached when ADCC-competent cells (effectors) or complement factors are mixed with the target cells in the presence of the anticancer	BMWP considers it premature to open the guideline too much for non-inferiority studies, even in an oncology setting. As discussed also in the biosimilar mAbs workshop held at EMA in October 2011, the starting point is an equivalence study, and deviations should be justified. Superiority, which would be a possible scenario within a non-inferiority setting (although very unlikely in a biosimilar setting), could imply dissimilar safety profiles, and more careful considerations may become necessary. These comments are acknowledged. The guideline text has been modified accordingly, i.e. the term "cytotoxic" was only used where appropriate, and otherwise changed to "anticancer" or deleted.

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	monoclonal antibody. Even in this case, IC50 can only be reached by increasing the fraction of effectors or complement factors, and not by increasing the concentration of the anticancer monoclonal antibody. In addition, the "cytotoxic" epithet and monoclonal antibodies are used only in the following broader context according to the scientific literature: • rituximab/trastuzumab/etc. + cytotoxic chemotherapy; • rituximab or trastuzumab mediated antibody dependent cytotoxicity; • rituximab or trastuzumab mediated complement dependent cytotoxicity. Moreover "classical" cytotoxic drugs have significant non-specific detrimental effects ("carpet bombing") on highly proliferative normal tissues (e.g. hair, epithelial cells in the gastrointestinal tract, bone marrow), but targeted mAbs do not exert non-specific toxicity to these tissues. Therefore, we believe that using "anticancer" instead of "cytotoxic" for the epithet of monoclonal antibodies throughout the wording of the guidance would be a better choice.	
18	*General comments on section 6, Extrapolation of indications* As regard as the extrapolation of indications, the Italian Society of Hematology and the Italian Lymphoma Foundation, would underline that the monoclonal chimeric anti-CD20 antibody has considerably improved therapeutic outcome in a series of B-cell lymphoid malignancies such as diffuse large cell non Hodgkin's Lymphoma, follicular and marginal non Hodgkin's Lymphoma, and Chronic	The BMWP considers that the design of a clinical development programme to establish biosimilarity follows the principle that differences between the biosimilar and the reference mAb should be detected, and it should be ruled out that subtle

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	Lymphocytic Leukemia (CLL). However, there are several differences in the mechanisms that account for the therapeutic effects in these diseases. Firstly, there is a huge variability in the CD20 expression among B-cell malignancies. In contrast to B-cell lymphomas, which uniformly express high levels of CD20, relatively low levels of CD20 are typically expressed in CLL, while the expression of CD20 is at intermediate level in low grade NHLs. Therefore, the monoclonal chimeric anti-CD20 antibody exerts its anticancer effects through more than one mechanism of action in these malignancies. The predominant mechanisms of anti-CD20-induced cell death are proposed to be the result of antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The relative importance of these mechanisms differ between CLL and B-cell non-Hodgkin's lymphomas (NHL). ADCC seems to be the predominant mechanism for the clearance of neoplastic cells in lymphomas, and Fc-gamma receptors are critical for the in vivo actions of anti-CD20 antibodies. The difference in response rates among NHL patients according to Fc-gamma RIIIa polymorphisms supports the importance of ADCC in the in vivo actions of the monoclonal anti-CD20 antibody. In contrast, particularly for blood-borne diseases, such as the leukemic-phase of B-cell NHL, in CLL, in vitro studies with the monoclonal anti-CD20 antibody have shown CDC to be more rapid and effective at inducing cell death than ADCC or apoptosis, and Fc-gamma RIIIa polymorphisms are not predictive for response. Complement activation may be important, as increased expression of complement inhibitors CD55 and CD59 resulted in resistance to anti-CD20 antibody in B-NHL cell lines and CLL cells. However caspase-3 activation and induction of apoptosis, using a pathway similar to that of fludarabine and other chemotherapeutic agents, appear to play a more important role in CLL than in B-cell NHL. In addition to the	differences or those not being detected by lack of sufficiently sensitive physicochemical and biological characterisation are of clinical relevance. The foundation of a biosimilar mAb development is an extensive comparative characterisation of all functional parts of the mAb molecule, i.e. differences for example in CDC or ADCC would already there be detected. One could consequently argue that different mechanisms of action in different cancers do not necessarily mean that there need to be studies in all of these when other data on the biosimilar mAb would demonstrate equivalent functionality. One needs to be careful to distinguish trial designs that detect differences between molecules and trial designs that would measure differences between disease entities. The BMWP considers that the current guideline text in chapter 6 covers the points put forward by this stakeholder, and that appropriate justification and consideration of the current state of knowledge is an integral part. The guideline has therefore not been changed.

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	efficacy of anti-CD20 antibodies in inducing a proapoptotic signal via the cell surface target structure, several studies have pointed out the activity of anti-CD20 antibody in promoting cellular responses against neoplastic cells. Indeed, it has been recently shown that the monoclonal anti-CD20 antibody promotes uptake and cross-presentation of lymphoma cell-derived peptides by antigen-presenting dendritic cells inducing maturation of dendritic cells, and allows the generation of specific cytotoxic T-cells that may have a long-lasting protective effect. As matter of fact, none of the many putative pharmacodynamics markers is highly predictive of response in lymphoid malignancies. Therefore, despite the draft guideline proposes that justification as regards to extrapolation between two or more indications may be possible based on extensive quality and non-clinical data base, we are convinced that similarity between the originator anti CD20 antibodies and the similar biological medicinal products should be demonstrated in separate clinical equivalence studies each aimed to test a specific indication of the similar product.	
19	We do appreciate that this Note for guidance based on a Risk Management based Approach for the development of biological containing monoclonal antibodies. This would allow the optimised development needed for a better access of patients to biosimilars. *Non clinical* The three steps demonstration is highly appreciated. Indeed, it allows establishing a first level of comparability accompanied by the search for differences that will be further explored by a falsifiability approach. The demonstration of comparability would	

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	be assessed by favouring pharmacological activity and potency over pure analytical data. This would also permit the demonstration of similarity of all facets of the mechanisms of action. By doing this, extrapolation of indications would be reachable and would then increase better access to patients. *Clinical* The use of a sensitive population is a fine way for targeting the risk for no similarity and therefore demonstrating similarity. We understand that the target therapeutic population and specificities of the identified risks for no similarity is to be taken into account. However, further clarification of how to define this sensitive population is needed.	A sensitive population is one where a clinical read-out exists that is discriminative enough to detect differences in treatments, and where as few factors as possible exist that impact on this treatment response or that interact directly with the treatment. An example could be the model of patients with renal anaemia and without major complications (such as severe/chronic infections or bleeding, or aluminium toxicity) for studying biosimilar erythropoietins: These patients have an absent or very low intrinsic production of erythropoietin (due to their renal condition), i.e. any leven of erythropoietin measured in plasma or acting on its target is only the pharmaceutical product and no

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	Procedure We would like to propose the possibility of granting a conditional MA approval for biological containing monoclonal antibodies, in order to bring the biosimilars as soon as possible to the patients in an affordable way. The safety of similarity could then be confirmed on the long run, thanks to dedicated pharmacovigilance tools, including RMPs. **A pilot phase could be implemented** for the next upcoming biological containing monoclonal antibodies during a relevant observation period frame. **An EMA/FDA coordination would be greatly appreciated**	endogeneous erythropoietin. Absence of infections etc. that would impact the primary endpoint (haemoglobin levels) by interference in haemoglobin synthesis even further strengthens this population. Therefore, the likelihood is high that differences between two study arms comparing a biosimilar to a reference medicinal product are attributable to real differences in the molecules and not to differences between patients. However, BMWP feels that this concept is not restricted to biosimilar mAbs but is applicable to all biosimilars. The BMWP will therefore discuss if further explanation should be considered for the revision of the general overarching guideline on biosimilars. Biosimilar medicinal products are not expected to fulfil the legal requirements for a conditional MA in particular with regard to the unmet medical need. This is without prejudice to the possibility of requesting the conduct of studies as a condition of the marketing authorisation. EMA and FDA are in contact by the newly founded biosimilar cluster :(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001282.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_event

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		s/news_and_events.jsp).
20	The guidance is highly scientific and appropriately permits the application of scientifically-driven judgement to individual products and situations. A flexible, case by case approach in guidance is welcomed by EBE, as it allows for the realities and diverse nature of the drug development process. However, the lack of detail on the non-clinical and clinical requirements and frequent recommendation to utilise the scientific advice procedure does not translate into transparent regulatory requirements for approval. EBE recommends, in addition to this general guidance document, product and/or class specific guidance, to detail with more specific issues in relation to establishing biosimilarity, and thus increase transparency.	This issue has been discussed at the EMA workshop on biosimilar mAbs in October 2011. Product or indication-specific guidelines are at the present stage considered premature due to the following reasons: - Although CHMP has given several scientific advices in this area, there is not yet a successful marketing authorisation of a biosimilar mAb while the guideline on biosimilar mAbs is finalized. Therefore, it is not yet known which concept is successful. - Giving too detailed guidance at the present stage may reduce flexibility and bind the hands of companies developing biosimilar mAbs too much. - The discussions on the circumstances when a PD endpoint would be acceptable as a substitute for efficacy data are ongoing; a prematurely issed guideline would have to take a more conservative standpoint. - A clearer picture on which patient populations,

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		endpoints etc. to study may exist for some, but not for all mAb products on the market. Issuing guidance for only a subset of products or indications could put too much emphasis on those where more experience exists. - Drafting of product-specific guidance as part of the current guideline would significantly prolong the publication of the final guideline text and would require another public consultation.
	Conjugated/radiolabelled mAbs would also benefit from a specific dedicated guidance.	Product or indication-specific guidance may be developed at a later stage.
	Overall, the guidance may be interpreted having an overall goal to generate and require only minimal amount of data to demonstrate similarity. EBE believes that the core aim should be to ensure that patient welfare is respected. This means ensuring that the benefit/risk ratio established by the innovator is attributable to the biosimilar. The plan undertaken by the developer should consider studies which one might routinely expect to demonstrate a high level of similarity (such as nonclinical and human studies) and where appropriate should justify the omission of any study based on scientifically justified arguments.	The BMWP does not see why this class of mAbs would require an own guidance, but will keep note of this comment for a later stage when the issue of indication- or product-specific guidance is considered.
	The guideline should acknowledge that that there will be differences between the innovator and biosimilar product, however the aim should be to establish a high level of similarity and not to demonstrate that the products are identical.	The BMWP considers that this is not a correct interpretation of the overall philosophy of the guideline. The guideline aims, as explained also in response to other comments, at helping establishing a development programme for a biosimilar mAb to establish biosimilarity with a scientifically appropriate dataset to reach this goal; not with the aim to require only minimal amounts of data. This is unfortunately a common misconception of the biosimilar concept. Likewise, the BMWP wishes to clearly state that patient welfare is not at all

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	Differences which could influence tolerability, immunogenicity and other aspects of product behaviour may not become evident in "simple" PK/PD evaluations. Since the patient is central to all drug development, as previously stated there must be confidence that the benefit/risk profile established by the innovator product can be attributed to the biosimilar. Therefore there must be sufficient data to establish this link. *CMC* The guideline should make reference to the related guidance for mAb biosimilars Quality aspects and should state that similarity from a quality point of view should have been established before design of an appropriate non-clinical/clinical pathway The guideline could be interpreted that in vivo non clinical testing should not be routinely applied to biosimilar products prior to dosing in man. EBE agrees that large scale comparative studies are unlikely to be valuable. However, due to the lack of ability to fully characterize the physico-chemical properties of the biosimilar and to gain complete understanding of the mechanisms of off-target toxicity of biological therapeutics, we recommend that all biosimilars undertake a limited repeat dose in vivo study in at least one animal species, i.e., in a pharmacologically relevant species, prior to human dosing. This should include at a minimum safety data with evidence of exposure and pharmacodynamic effect, and should be mandatory prior to clinical trials of a biosimilar (indeed would be likely to be considered as required by national competent authorities assessing clinical trial applications), in order to safeguard human subjects. The purpose of this study is to detect any significant unpredicted off target toxicity.	compromised by following the principles of biosimilarity. Correct, therefore clinical data is normally required (please see guideline text). Please see above. There is already reference to this guideline (lines 100-101 of

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	This approach is consistent with recently published guidance on testing of biosimilar ESAs. *Clinical* Similarly, EBE's position is that an adequately powered head to head clinical study with predefined and clinically justified equivalence margins is needed to establish a high level of similarity, to determine efficacy and safety outcomes to allow the conclusion that the benefit/risk profile established by the innovator is attributable to the biosimilar. However, any deviation from this position should be justified. Regulator-accepted, scientifically valid, surrogate endpoints and appropriate confidence intervals are essential in the assessment of the biosimilar. Investigation must allow for establishment of comparable efficacy, safety, immunogenicity, establishing similar benefit/risk and thus allowing extrapolation to established clinical benefit. This is essential to protect patient safety. Any indications claimed by a biosimilar (and similarly endpoints utilised to support this) must have been approved by EU regulators, and the use of the biosimilar in the indication in question must be established as having a positive benefit/risk ratio overall. EBE understands the most sensitive population to be one where you are most likely to be able to detect relevant differences between the innovator product and the biosimilar. EBE would like to request more guidance/clarity on how to define this homogenous/sensitive population. The guideline lacks clarity on the specific implications for Product Information (Summary of Product Characteristics, Patient Information	the draft guideline).

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	Leaflet) of monoclonal biosimilar antibodies and how extrapolated indications should be described. EBE recommends explicit and transparent communication on the data on which the approval is based, and where extrapolation is made from the innovator product. Recognising that, in a post-marketing setting, it will be important to attribute safety and efficacy outcomes to the originator and biosimilar product, each type of product should be uniquely identifiable at the level of the Prescriber/Pharmacist/MAH to enable this. EBE recommends that this principle is clearly stated in the guideline in accordance with good pharmacovigilance practice. *Concluding remarks:* Conjugated monoclonal antibodies and radiolabelled antibodies should be out of scope of this guideline due to their complexity. Since the primary mode of action requires a non-biological (small molecule or peptide) component, and therefore there would be no premise that the products should have the same pharmacology or pharmacokinetics. EBE recommends an additional guideline on how these products should be characterised. Line 117 concludes that next generation biologicals are beyond the scope of this guideline. Sponsors will always be able to apply principles laid down in guidelines to other cases and discuss with agencies in scientific advice processes. Therefore the last two sentences (starting from "Nevertheless, principles laid down.." should be deleted. In addition, EBE would welcome an explicit statement to note that products with different amino acid sequences cannot be biosimilar. EBE suggests the following edit to line 117: " As a principle biosimilars	BMWP considers that this is covered by the current guideline text. The requirements for acceptance of PD markers as sole or major contributor to the clinical comparability exercise are currently under discussion. The current guideline text is in the opinion of the BMWP flexible enough. Any product to be licensed must have a positive benefit/risk estimation, including biosimilars. This does not have to be reflected in the guideline text. See further above in this document.

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	must have the same amino acid sequence as the reference molecule” Overall, EBE would recommend some simplification of the executive summary as it is, in parts, duplicative to the main text. EBE recommends a further workshop to discuss points in relation to these comments, for example, to give detailed input on class/product specific guidelines. EBE would be willing to give input on topics for discussion if such a workshop is adopted.	This is not a scientific aspect and therefore outside the remit of the guideline. SmPC etc. will be decided by the CHMP at the time of MAA. This will indeed be done with the EPAR after MA. See further above in this document. Besides this, there is already recommendation to follow such developments (lines 463-465). BMWP considers that at the present state it is premature to

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		include or exclude conjugated mAbs. Some considerations and principles in this guideline may well be applicable. BMWP therefore considers that the guideline scope should be silent on this aspect. BMWP disagrees. It is important to state that principles may be valuable, and that regulatory authorities are willing to discuss such cases as part of a scientific advice procedure. The issue of identical amino acid sequence is a general aspect, not only related to mAbs, and therefore a discussion on this will be held in the margins of revision of the general biosimilar guidelines. The executive summary is meant to summarize the most important aspects of the guidance text. Duplication is therefore unavoidable.
21	• Roche appreciates the possibility to be involved in development of the guidance on biosimilar monoclonal antibodies (mAbs). We agree that the selected approach in each case should be based on scientific considerations and available experience with these	See similar comments elsewhere in this document. BMWP agrees that the database for clinical efficacy and safety for a biosimilar mAb needs to be sufficient at the time of MAA, but the way to reach this goal depends on the particular mAb and

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	complex protein products, without compromising safety. As a principle, adequately powered head-to-head efficacy and safety studies comparing the biosimilar and reference mAbs in relevant indications should not be waived, particularly since there is currently no experience on biosimilar mAbs. • Since the patient is central to all medicinal product development, there needs to be confidence that the benefit / risk profile established by the innovator product can be attributed to the biosimilar product. Therefore, there must be sufficient data to establish this link. This entails the use of surrogate endpoints that have been deemed valid for approval of innovator products. Clinical trials should be set up using equivalence designs. In patient populations/ indications, and where there is curative potential, biosimilarity should be demonstrated. Equivalence margins in those settings should be tighter as opposed to palliative settings • The proposed guideline is provided to lay down the non-clinical and clinical requirements for all mAb products. We agree that an overarching guideline is a good first step in setting the frame for registration of these important products, however, to guarantee transparency and clarity of requirements, product specific non-clinical and clinical guidelines are requested also on specific classes of biosimilar mAbs, since the non-clinical and clinical requirements depend on the given mAb and the indications sought. It should be also taken into account that the EMA biosimilar guidelines are used as reference documents also outside of the EU, by both regulatory agencies with relatively little experience in evaluation of biological products including biosimilars as well as manufacturers not so familiar with high standard	the overall dataset at the time of approval. We do not agree that the guideline aims at setting minimal or low standards for the development of biosimilar MAbs. On the contrary, the GL aims at setting adequate and sufficient requirements needed for a) safeguarding safety of patients and volunteers and b) establishing biosimilarity between reference and biosimilar product. A requirement to minimise the use of animals following from the 3Rs principles does not imply that standards will be lowered or a minimal approach would be acceptable. Instead, a rational and informed strategy is proposed to obtain the required information needed to come to a decision. Please see similar comments elsewhere in this document.

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	regulatory requirements. Consequently, clear guidance documents with less room for incorrect interpretation are requested. ○ In the product specific guidance useful additional advice could be given on the design and number of the given non-clinical and clinical trials as well as inclusion of patients from different disease states. Potential extrapolation of similarity at several levels should be further discussed in the product specific guidelines. These include guidance on *in vitro* to *in vivo* extrapolation, specific design of comparative PK studies for a particular product, PK and PD similarity to efficacy/safety extrapolation, cross-indication extrapolation, and cross-population extrapolation. It should be stressed that any extrapolation should be fully justified. Further, it is clear that extrapolation of immunogenicity between indications is usually not appropriate. ○ We also think that suitable endpoints could be addressed in more detail in product specific guidance. In our opinion only validated endpoints should be used as primary evidence of biosimilarity. ○ Amount of patients required within Europe should be stated in the guidance. • The guidance may be interpreted having an overall goal to generate and require only minimal amount of data to demonstrate similarity. We strongly disagree with this approach. Because of the current lack of experience with biosimilar mAbs we think that it is premature to set low standards just to make the biosimilar regulatory pathway feasible for mAbs. To ensure patient safety,	More detailed guidance on the overall concept of biosimilars is available in the general biosimilar guidelines, which should always be read in conjunction with a more specific guideline on biosimilars (Please see references in chapter 3 of the final guideline). Please see above as regards product- or indication-specific guidance. As regards inclusion of different disease states, this is covered in the current draft, since the focus is on a homogeneous and sensitive patient population rather than different disease states.

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	we suggest that robust data should be required also by the guideline, and that EMA should then potentially revisit the requirements after the first biosimilar mAbs have been on the EU markets for an adequate period of time. • The guidance would benefit from a clear high level statement that head-to-head studies designed to demonstrate equivalence are needed. It should be also stressed that adequate pre-approval comparative safety and immunogenicity data from the clinic are needed in all relevant indications. The proposal to apply a conditional type of approval to biosimilar mAbs is regarded as questionable. It should also be made clear that the primary structure of the biosimilar mAbs has to be the same as the primary structure of the reference mAb. • The current text uses the terms "might" and "may" in several places. This wording makes the proposed regulatory requirements unclear to the reader. The guideline might also benefit from restructuring into more focused sections – part of the draft document is difficult to follow also due too long paragraphs and sections. It would also good to clearly differentiate between when the text refers to non-clinical PD, and when to human PD studies. • Since biosimilar mAbs will be approved based on an abbreviated dossier, and may have fewer indications and/or routes of administration than the reference product, we request that the product information be explicit and transparent about which data are based on use of the biosimilar, and which data are	Please see comment elsewhere in the document. The goal is not to generate a minimum dataset or to set as low hurdles as possible, but a scientifically suitable dataset to establish biosimilarity. This is already included in line 323 of the draft guideline ("parallel group comparative clinical trial(s), (...) normally equivalence trials"). Please see comments elsewhere in this document. As regards the safety database, lines 420-423 of the draft guideline are discussing this point as regards all relevant indications etc.

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	extrapolated from the reference mAb product More detailed guidance on naming of biologics should be provided to support traceability. In addition to the use of specific brand names for all biologics, we suggest that the agency should ask the biosimilar mAb applicant to apply for a new INN (Greek suffix) from the WHO INN in cases where differences in post translational modifications between the reference mAb and the biosimilar mAb cannot be excluded.	The terms "might" and "may" are in the usual language of scientific guidance deliberately chosen for situations where the guideline sets a certain expectation, but where it allows for deviations if appropriately justified. As regards SmPC, naming etc. please see related comments elsewhere in this document.
21	General comments on Section 4, Non-clinical studies SUMMARY • An animal safety study should generally be mandatory prior to clinical trials of a biosimilar, in order to safeguard human subjects. This mirrors what is done to enable any clinical trial/FIM administration. • Additional factors which may drive the need for animal testing should be included in the guideline (e.g. situations where data from *in vitro* assays or the assays themselves are inadequate, where there is a narrow safety margin with the originator, when a	Please see previous comment with respect to the need for toxicology studies on page **Error! Bookmark not defined.**. The Guideline does indicate that there could be a need for *in vivo* data if quality and in vitro data are insufficient to draw a conclusion. This would generally be a need to establish PD and or PK-related information. A narrow safety margin points to the occurrence of exaggerated pharmacology at doses not greatly exceeding the therapeutic dose. Generally, the potency ought to be tested and compared using *in vitro* assays, which usually should be sufficient to establish

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	different expression system is used for manufacturing). • Clear selection and qualification criteria for analytical and *in vitro* assays are lacking in the guideline and should be included. Clarity on the acceptable level of differences would be helpful. The draft guidance implies that there are circumstances in which analytical and *in vitro* characterization data would be sufficient to enable entry into human trials. We believe that current analytical and *in vitro* methodologies do not provide sufficient information to properly assess the potential *in vivo* safety and efficacy of mAbs prior to First-in Man trials, and that data from these analyses do not provide an appropriate level of information on structure function relationships. Rather, *in vitro* characterization data are best used to determine the scope of further *in vivo* assessments, or to refer to *in vivo* assessments done previously. In addition, some of the key quality attributes of the biosimilar mAb product such as process and product related impurities and product related substances will differ qualitatively and quantitatively in comparison to the reference product. As has to be done for any biotech product, the biosimilar manufacturer will have to establish acceptance ranges pre-clinically and clinically. As concluded from the draft guidance, comparative human trials are always required in order to demonstrate similar efficacy and safety, even if analytical and *in vitro* similarity have already been shown. However, it is difficult to understand why a comparative animal study (e.g. PK/PD with tox. evaluation) should not routinely be requested, as data from this will safeguard patients in clinical trials. As for any product, we suggest that some non-clinical *in vivo* toxicology data are necessary prior to entry in human. We do not	similarity, thus obviating the need for animal studies. Presence of relevant quality attributes that have not been detected in the reference product (e.g. new post translational modification structures) is included in the Guideline as an important criterion. We believe the final Guideline is as explicit as possible in identifying the circumstances where no *in vivo* studies would be required.

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	agree that potential for results that are difficult to interpret is appropriate justification for not requiring *in vivo* animal studies before entry in human. Comparative non-clinical safety, PK and PD studies can provide critical information to ensure adequate safety prior to clinical testing for biosimilars. The dosing regimen, dose levels, study duration and route of administration should be carefully considered to best identify changes in anticipated safety or pharmacodynamic profiles. PK/PD and safety evaluations should be conducted in a relevant species. In this regards, the following points should be considered: ○ The Guidance should be explicit about the exceptional circumstances under which all animal studies can be omitted (examples) and should explain how the biosimilar manufacturer can then assure clinical safety for First-In-Man trials. Process, quality, physico-chemical attributes or post-translational modifications won't be identical between the reference and the biosimilar mAb and these factors can impact dose-response relationships in ways that cannot be predicted from *in vitro* data (impact on biodistribution/PK, different (off-target) binding pattern/effects etc.). The choice of assays will define, and may limit the quality of data generated. Hence, more clarity on the selection and qualification of analytical and *in vitro* assays is necessary. It should be clarified which level of difference is acceptable. If a risk-based approach is to be used for evaluation of non-clinical safety of the biosimilar mAb, it would be advisable to get more	

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	information on risk categorization depending on the mode of action of the mAb (e.g. based on the risk for adverse exaggerated pharmacological *in vivo* effects, the role of effector function driven activities for cell-based targets *in vivo*, expression of target in healthy animal species (if any) vs. disease state, etc.)	
21	General comments on section 5, Clinical Studies Section 5.1 and 5.2 (Pharmacokinetics and Pharmacodynamics) SUMMARY • There needs to be confidence that the benefit / risk profile established by the innovator product can be attributed to the biosimilar product	This comment (which was also sent in by other stakeholders) is unclear. It is clear that any medicinal product has to have a positive benefit-risk at the time of approval. This is not different for a biosimilar. This does not have to be stated in this guideline.
	• A waiver on a phase III equivalence study should only be applied if scientifically justified and the *in vivo* PD endpoint is clinically validated • With current state of the art techniques, there are no good *in vivo* PD markers for clinical outcomes in oncology or Rheumatoid Arthritis (e.g. B cell depletion) • PK equivalence studies are necessary but are not sufficient to	The choice and acceptance of PD markers and/or surrogate markers as primary proof for biosimilarity is subject to justification and the respective dataset.

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	show similarity • Clarity is needed as to what a homogeneous and sensitive population means. It is often a challenge in determining the subgroups of patients who respond best to a treatment as often such subgroups have not been validated in prospective, randomized studies.	See similar comments elsewhere in this document
	• The document suggests that when a head-to-head clinical PK/PD study shows similarity, comparative clinical efficacy and safety studies may not be needed. Clarity is required about where *in vitro* and *in vivo* PD markers are valid endpoints. This is a concern as there is no strong scientific evidence that similar PK and PD would translate to similar efficacy and safety in oncology and rheumatoid arthritis. Many available PD markers have low predictability for efficacy, and safety events. For example, response rate in oncology is not an accepted regulatory endpoint as there is uncertainty regarding its use in the prediction of outcomes.	Prediction of outcomes and correlation of a marker like response rate with survival is relevant for establishing benefit for a novel medicinal product, but may be suitable for a biosimilarity exercise, as explained elsewhere in this document.
	Similarly, suppression of B-cells does not correlate to duration of effect in RA. Quantification of safety signals can only be assessed in adequately powered clinical trials and post marketing. This is true for immunogenicity assessments as well. Since the methods for evaluation of PK/PD and immunogenicity will potentially be different than those that were originally used for the reference therapeutic, these studies for similarity will need to be run side by side using the same well characterized bioanalytical methods so that a fair comparison can be made based upon data from the	BMWP supports this comment. The guideline has been

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	same assays. • The clinical pharmacology section of product information for the reference mAb is based on thorough clinical investigation. Biosimilarity, if established by one clinical comparative PK study should not enable automatic claim of the full-spectrum of clinical pharmacology data in the product information. Information regarding drug-drug interactions, special population PK, dose modification, PK dose and time dependency, dose-response relationship, etc. should not be assumed to be "biosimilar" without appropriate clinical comparison. Furthermore, since the dose-response relationship between various diseases and indications may be different, a dose-response relationship established in one indication cannot always be extended to another. Section 5.3 (Clinical Efficacy) SUMMARY • Selected criteria to proof clinical similarity should be tailored to the benefit brought by the reference product and customized for each indication, specially where cure is the expected treatment outcome • Clinical safety and efficacy trials should be considered a normal route for investigating similarity, as there are no validated *in vivo* PD surrogates at this date for mAb products approved in oncology and rheumatoid arthritis (RA) indications • Equivalence design should always be implemented, as non-inferiority will not exclude superiority, which could imply a	amended to more clearly state that PK/PD, safety and immunogenicity assessments will have to be comparative in nature, which implies use of the same methodology within this trial. A direct comparison is therefore possible. See comments on the SmPC elsewhere in this document.

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	different safety profile • Equivalence confidence interval should be pre-defined statistically and clinically, and justified and based on the pivotal innovator data Draft guidelines establish that if dose comparative and highly sensitive PD studies cannot be performed convincingly showing similarity in a clinically relevant manner, similar efficacy should be demonstrated in adequately powered comparative, normally equivalence trials. Roche believes that equivalence clinical trials should be considered a normal route for investigating similarity in oncology and rheumatoid arthritis (RA) indications, and does not believe that comparative human PK/PD studies alone are sufficient to avoid efficacy and safety clinical trials in those indications as there are no existing validated *in vivo* pharmacodynamic (PD) surrogates at this date for mAbs approved in oncology and RA indications. As a consequence, Roche believes that product specific guidance would provide clarity on whether there could exist any circumstances where clinical efficacy studies can be avoided. Selecting scientifically appropriately sensitive humans models and study conditions (whether licensed or not), may be problematic not only technically but also from an ethical standpoint. For non-licensed indications of the reference product no information for PK exists and thus steady state PK is not known for the reference product. No information on safety profile is available and the parallel group investigations are performed in patients simply for the investigation of similarity proof, and if it fails, patient have no benefit. Establishing equivalence margins based on *in vivo* PD markers or non-licensed	BMWP considers that this is what is written in the guideline: The starting point is an equivalence trial (expressed by the word "normally"), and deviations would be possible only with sound scientific justification and adequate data.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	indications is problematic due to unknown and anticipated impact on treatment outcomes (for example progression free survival or overall survival in oncology). Section 5.4 (Clinical Safety) SUMMARY • Clarity on the type and size of pre-approval data base is required for cases where similarity is established based on dose comparative and highly sensitive PD studies • Determining the adverse event profiles of the biosimilar and establishing similar safety pre-approval requires more clarity/specification on the nature incidence and outcome of the adverse events. As the rations of AEs may vary between the reference product and the biosimilar, enough data to quantify the AEs will be needed • Immunogenicity assessment generally can only be done in clinical trials and extrapolation across patient populations, indications or different treatment regimens may not be possible The guideline touches upon most of the important items relating to clinical safety and pharmacovigilance but in a rather uncoordinated way. It would help the reader to have clearly separated topics in the	BMWP strongly recommends that in such scenario the applicant seeks a scientific advice procedure upfront. . The reasoning for this scenario is that if there was, in theory, a very sensitive model which is widely used in the medical community (based, for example, on publications of study data peer-reviewed journals) but not formally licensed, then this could (pending agreement with regulatory authorities) be considered as a possible model from a scientific perspective. PK data etc. would be generated in a comparative manner, and therefore would become available with the biosimilar mAb MAA submission.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	clinical safety section (e.g. overall safety evaluation with associated implications for the longer term safety data collection because of the shorter clinical programme and smaller safety database; overall safety evaluation should discuss implications of the overall different safety profile of biologicals with Adverse Events mainly due to their pharmacodynamic effect and of course immunogenicity with specifically mentioned infections as a safety problem often seen with biologics – examples of reactivation of tuberculosis or PML; immunogenicity). Despite the fact that the biosimilar and reference drug can show similar efficacy, the biosimilar may exhibit different safety profile in terms of nature, seriousness or incidence of adverse reactions. However, the data from pre-authorisation clinical studies normally are insufficient to identify all potential differences. In addition, all biotechnology products, including biosimilars have a potential to cause immunogenic events that may sometimes take years to develop, may only occur infrequently. Although, only long-term use in large numbers of patients will reveal a greater number of any clinical differences (e.g. for immunogenicity) it should be discussed in the guideline what the appropriate size of the safety database should be at the time of approval. Consequently, it is likely that the safety database of the biosimilar will not be adequately extensive for a fully quantitative comparison of the frequency of the AEs. In this case, the SmPC of the biosimilar should be required to prospectively collect the safety events such that a comparison of the rates can be made after a specified time (e.g. 2	Some clarification has been added to the guideline. BMWP considers that differences (if any) in more rare adverse events will not feasibly be collected before authorisation. This is reminiscent of the situation of a manufacturing change of a biotechnological medicinal product where the only feasible way to grant such change is to have a post-authorisation follow-up. This would be likewise required for a biosimilar, depending on the strength of evidence provided at the time of MAA.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	years post launch).	
21	General comments on section 6, extrapolation across indications SUMMARY • Extrapolation from metastatic indications to adjuvant should not be allowed as the risk to the patient in a curative setting far exceeds the benefit. Adequate Phase III studies should be done in the adjuvant or curative settings. • Extrapolation of indications requires well-balanced assessments and is not possible in many cases as with current state of the art techniques, there are no good *in vivo* PD markers for clinical outcomes. As a consequence Roche believes that clinical trials would be required and extrapolation would not be possible between RA and oncology indications for rituximab, and metastatic versus early breast cancer setting in the case of trastuzumab • Clarity on the type and size of pre-approval data base is required for cases where extrapolation across indications is established based on overall evidence and proof of biosimilarity The draft guideline proposes that justification as regards to extrapolation between two or more indications may be possible based on extensive quality and non-clinical data base, including potency assay (s) and *in vitro* assays that cover the functionality of the molecule. As indicated above and with today's knowledge, there are	BMWP comment: The idea of the concept is that the totality of data, together with a strong proof of similarity in a clinically sensitive model to detect differences (if any), will allow for extrapolation, together with a thorough scientific justification. To require clinical data "by default" in the adjuvant setting (which is not necessarily curative) would deviate from this concept and could potentially put a biosimilar mAb development at risk, would this model not be sensitive enough to detect differences and therefore falsely suggest similarity. The final choice of the sensitive model is up to the Applicant, and BMWP can at this stage not recommend more specifically a certain model. Important factors to be considered would be PK considerations (potentially easier in an adjuvant setting due to lack of interference of excess tumour antigen), available endpoints (potentially easier in the metastatic setting due to measurable tumours in case of response rate as an endpoint) etc.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	inherent limitations with the utilization of *in vitro* assays and lack of validated *in vitro* PD markers as surrogates of efficacy endpoints. Product specific guidance would provide clarity on whether extrapolation from one therapeutic indication (oncology) to another (example, RA) should require separate PK/PD, safety and efficacy studies as there are also differences in dose/regimens, mechanisms and immunogenicity. In the case of Anti-CD20, extrapolation from oncology to RA is not possible as the dosing interval and duration of activity is entirely different, and at this date there is not a validated *in vitro* PD surrogate of clinical outcomes. In addition, clarity is required whether clinical efficacy data in metastatic disease can be extrapolated to the adjuvant setting. Guideline should require clinical trials unless there is a justification. A potential concern with the concept of extrapolation is that the risks for using a biologic may differ in various patient populations as there may e.g. be differences in the level of immunocompetence (e.g. between patients with cancer and those with other diseases). This is particularly exemplified by the Infliximab case (different levels of immunogenicity in different indications and populations) Generally, in order to mitigate and balance the risk associated with extrapolation of indications with biosimilars, similarity should be demonstrated by any means in the indication where the treatment provides cure. Extrapolation to other indications may be granted in case of proper justification e.g. high degree of molecular similarity, same expression system, same mode of action, same drivers of PK etc.	

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
21	General comments on section 7, Pharmacovigilance Plan and Post-authorisation follow-up • Maximum transparency about biosimilar product data is required Product information should distinguish data sources (originator, biosimilar, extrapolation, others) • MAb biosimilar products should have unique identity or name and prescriptions made by brand name • Interchangeability and substitution are not addressed. More transparency is required as if not properly managed it will dilute safety database as well as hamper the pharmacovigilance activities Because biosimilars are not equivalent to the reference product and because unique efficacy and safety data will be available, the product information should include these data. PI should distinguish data sources (reference product, biosimilar, extrapolation, others). There should be cross-reference to the originator's PI Warnings and Precautions and to long term safety sate monitoring/ collection. Labeling should also clearly indicate which indications are based on extrapolation of data, and which are based on clinical data for the biosimilar because physicians, pharmacists and patients should be aware of the clinical data supporting an indication and of the instances in which indications are based on extrapolation of data.	See comments elsewhere in this document.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	It is important in the post-approval phase to distinguish easily between the biosimilar product and the reference product so that it is clear which product a patient has received. Product naming is covered, but other means of improving traceability could be mentioned: unique generic name, recording the lot numbers, etc Technical measures could be: - tear-off sticker on the pack - 2-D barcodes A paragraph on substitution and the risks associated with this practice (although not endorsed by the EMA and prohibited in many countries) could be beneficial as inappropriate substitution could potentially occur when prescribers do not understand the potential risks involved and when the distribution systems allow or encourage automatic substitution. Substitution should be viewed as a change in clinical management. Also, to ensure that an accurate, 'un-polluted' safety database is established, substitution should be prohibited	
21	<u>The guideline does not contain any language around</u> 1. Product labeling PI should distinguish data sources (reference product, biosimilar, extrapolation, others). There should be cross-reference to the originator's PI Warnings and Precautions and to long term safety sate	See comments elsewhere in this document (outside the remits of a scientific guideline, and up to CHMP decision at

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	monitoring/ collection. 2. (Automatic) Substitution Although the EMA's position is that "since *biosimilar and biological reference products are not identical, the decision to treat a patient with a reference product or biosimilar medicine should be taken following the opinion of a qualified health professional*", it would be beneficial to restate in this guideline that physician should be involved in the decision. More transparency is required as if substitution is not properly managed it will dilute safety database as well as hamper the pharmacovigilance activities. 3. Interchangeability This is defined as the clinical practice of switching from one medicine to another that is considered equivalent, in a given clinical setting. This decision can only be made by the physician choosing an alternative within a certain class of drugs.	the time of MAA). Please see comments elsewhere in this document (outside the remits of the European Medicines Agency)
21	General comments on immunogenicity for consideration Although reference is made to the CHMP immunogenicity guidelines, we believe that the biosimilar mAb guideline should be more specific about what is needed for an assessment on immunogenicity. It is also expected that the EMA guideline on immunogenicity on mAbs currently under development will give relevant, clear advice also on the development of biosimilar mAbs. The current guideline highlights one	BMWP agrees that some more clarification and a reference to the guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use is useful. Here, Applicants will find information. Reference to scientific papers as requested here is usually not made in CHMP guidelines,

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	factor that may increase the risk of immunogenicity (usage of a different expression system) but there may be other factors which should also be considered. The measurement and assessment of immunogenicity of mAbs is technically challenging, and by now there are several "Industry White Papers" and papers from regulators in the literature which could be referred to here (Mire-Sluis et al 2007, Koren et al, 2009, Buttel, et al 2010). The assessment of immunogenicity between the reference mAb and a biosimilar is dependent on the anti drug antibody assay format and immunogenicity strategy, therefore some discussion on the anti drug antibody strategy and assays might be helpful. If the biosimilar sponsor's anti drug antibody rate data for the reference molecule from their side by side clinical trials are very similar to the data that were obtained for the reference molecule in the same indication/context, this would be an indication that a quality methodology was used. Another concept worth mentioning in short in this guideline is the potential impact of non-neutralising antibodies vs. neutralising anti-therapeutic anti drug antibodies. It is important to mention that even non-neutralising antibodies can affect the pharmacokinetics of a product and thereby influence efficacy indirectly, and also have impact on claims of biosimilarity.	also because such a reference list would soon be outdated and it would never be exhaustive.
22	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies." BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative	

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	healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. The Guideline in general is useful and contributes guidance to those planning to develop biosimilar versions of existing originator monoclonal antibodies. The Guideline attempts to cover a very wide and diverse group of products, including some novel types of monoclonals not yet envisaged as potential biosimilars. For this reason it has to allow for a range of circumstance and be potentially very flexible. However, this partly limits the Guideline's usefulness and may leave sponsors requiring further specific scientific advice in many circumstances. It may be more appropriate to revisit the concept of having sub-class specific sections/appendices or providing additional details rather than referring to a case-by-case approach in so many places. We request that the EMA be clear with regard to informing applicants whether or not this is an overarching Guideline, to be followed by more detailed guidelines for specific mAbs, similarly to what has been done for less complex biosimilars. If more specific guidelines are not envisioned, then this one may require additional detail and boundaries in order to effect efficient development. The Guideline offers a pathway for approval of a biosimilar monoclonal antibody. However, the benefits of this approach, where scientifically justified, will not be realised for sponsors unless they are universally/globally accepted. For example, if a sponsor meets the EMA expectation (described here) for a product that no in vivo data need be generated and extrapolation is possible to a number of indications, but this is not agreed with the United States Food and Drug Administration (FDA), then these additional studies will still be	Please see comments elsewhere in this document (no indication/product-specific guidance at the present stage).

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	required. The acceptability of the risk based approach for non-clinical testing will also be critical for the review of proposed Clinical Trial Applications (CTAs) by national regulatory authorities. The omission of quality expectations and case-by-case inclusion of structural alterations for improved or different clinical performance leaves applicants unclear on the basis for abbreviation of study (same CDR, same epitope, or highly similar structure across all Critical Quality Attributes (CQAs)). The Guideline does not address the 'aggregate' minimal standard across non-clinical/clinical sections. Since flexibility is offered in a number of areas, the Guideline does not address whether a minimal approach in all areas would meet the agency's tolerance to allow abbreviated study. This may be ambiguous to companies without EMA expertise and minimum vs. expected standards should be clarified. It should be clear that the reference product for a biosimilar application must be CHMP approved. It is also not clear if the reference product for a biosimilar application must be CHMP approved. This should be clarified, as national approvals and approvals in other regions can be for mAbs manufactured under slightly different processes that could impact biosimilarity considerations. The Guideline would be more useful if it contained fewer generalities throughout the clinical section. It would also be helpful to know how this Guideline relates to previous guidelines or if this supersedes the earlier documents (e.g., cross-reference with Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use). Also, we find the Guideline as phrased could create the misimpression that not all non-clinical stages are necessary; it would be helpful to	EMA and FDA have formed a Biosimilar Cluster to exchange views on biosimilars. Please see comments elsewhere in this document.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	have clarification that a stage is considered unnecessary only if it is scientifically inappropriate.	Please see comments elsewhere in this document. The aim is not a "minimal approach" but a scientifically sound approach to establish biosimilarity by respective clinical trial designs. This is an aspect that rather belongs to the overarching biosimilar guideline, since it is not specific to mAbs. As such, it is covered in the overarching guideline. The reference medicinal product needs to be authorised in the EU/EEA. From a scientific perspective, such slight differences would be detected by the head-to-head comparison that is obligatory for a biosimilar mAb development. BMWP considers that the more general aspects are nevertheless important, since they introduce the principles in the current thinking of the CHMP around biosimilar mAbs. Cross-reference to Immunogenicity guideline for mAbs added. Non-clinical part has been revised (Please see respective comments/sections).

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
22	General Recommendations: We suggest that the Guideline articulate core principles in order to define the boundaries of 'biosimilarity' for monoclonals. Language like "comparable safety with respect to pharmacologically mediated adverse events could also be considered as a measure of biosimilarity" (emphasis added) is unclear and leads an applicant to wonder if improved safety profile or increased purity without impact to efficacy would disqualify biosimilarity. Declarative statements on boundaries of 'biosimilarity' will assist all manufacturers in developing strategies and reducing waste. We also strongly suggest that the Guideline clarify that an abbreviated pathway is only available for monoclonal antibodies that meet the standards of similarity outlined in the EMA existing Guideline for quality aspects of biosimilars, including but not limited to the same primary structure. Also, even though the pathway is validated by the innovator, humans may have not been exposed to the specific biosimilar molecule and unique manufacturing process. An adequate (although abbreviated), non-clinical evaluation is needed before human testing. We ask that the guideline define an overall minimum data standard or acknowledge that the minimum across all aspects of nonclinical and clinical evaluation is not acceptable.	This sentence has been reworded. References included. Please see comments elsewhere in this document.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
		Please see comments elsewhere in this document.
22	The Guideline appears to introduce many refined concepts, and some entirely new concepts, of a general nature (we identify these concepts in the section "Specific Comments on Text", below). This may not be the optimal or most transparent mechanism to revise the basic emphasis or logic of existing nonclinical and clinical guidelines, especially when many of the issues concerned are neither specific to, nor even specifically relevant to mAbs. We recommend these discussions (absent those not within the appropriate scope for biosimilars) be addressed in upcoming revisions of the overarching guidelines. Where the Guideline is general in nature (e.g. concerning matters not specific to mAbs) it is proposed that the EMA should provide clarifying statements, either in the Guideline itself or in a separate document. Such statements should cross-reference the existing non-clinical and clinical guideline and clarify either that: 1) The new Guideline is intended to be consistent with the existing Guideline, with elaborations on certain points, or 2) Where something significant has changed, the Guideline should be very specific as to the justification for departure from the current guideline (either it is specific to mAbs or the EMA intends to revise the non-clinical and clinical Guideline for a given reason). Without these additions, it appears that there are two "general" Guidelines on nonclinical or clinical requirements, with no justification as to why a different set of principles should apply to mAbs.	The ideas put forward by this guideline will be part of the discussions around the revision of the general guidelines of biosimilars. They will, nevertheless, be kept in this guideline on biosimilar mAbs, since BMWP considers them relevant. The BMWP feels that there is no contradiction to the general guidelines, and therefore considers that deviation from the current format of the biosimilar mAbs guideline will be confusing and time-consuming (since it may also require another round of consultation).

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
22	Overall, the Guideline does not adequately communicate that a biosimilar will differ to varying extents from the innovator product in chemical and manufacturing-derived attributes and/or formulation which could influence tolerability, immunogenicity and other aspects of product behaviour not evident in "simple" PK and PD assessments. As a result of this omission, the Guideline could be interpreted to convey that because a manufacturer calls something biosimilar based on the most obvious characteristics, it will be so when examined in depth. Unfortunately, the Guideline also leaves open the possibility of a somewhat superficial non-clinical and clinical evaluation in some circumstances. Our comments below emphasize that stringency in the evaluation of a biosimilar product is appropriate given the exigencies of the production and formulation of a biologic product and the opportunities for differences from the innovator product when only the protein's structure is considered as a primary determinant of biosimilarity.	BMWP disagrees. The concept, as repeatedly discussed in this comments document, is to establish biosimilarity, and not benefit (which has been established by the originator). The guideline does not communicate in a large extent about differences, because (1) this is not an aspect specific to mAbs, and (2) more than non-significant differences would put into question if a given mAb candidate is indeed a "true" biosimilar. To talk about potential differences could be prone to misunderstandings, i.e. that such differences would be acceptable for a biosimilar. BMWP considers that cross-reference to the general guidelines on biosimilars will be helpful in this respect.
22	The Guideline could be interpreted as saying that in vivo non clinical testing should not be routinely applied to biosimilar products prior to dosing in man. We agree that large scale comparative studies are unlikely to be valuable. However, due to the lack of ability to fully characterize the physico-chemical properties of the biosimilar and incomplete understanding of the mechanisms of off-target toxicity of biological therapeutics, we recommend that all biosimilars undertake a limited repeat dose in vivo study in a pharmacologically relevant species prior to human dosing. The purpose of this study is to detect any significant unpredicted off target toxicity and does not need to be comparative in nature. This approach is consistent with recently published guidance on testing of other biosimilar classes.	Please see previous comments and also discussions in the non-clinical sections.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	The anticancer target is identified as a special class of mAb that needs special considerations (section 5.1.4). However, the scenario could potentially apply to any indication/therapeutic area where drug effect and PK are inter-related, i.e., PK is affected by PD. As such, the section dedicated for the anticancer treatments could apply to other biologics from non-oncology indications. Therefore, additional language to cover a wider array of indications, e.g. beyond oncology, will be beneficial. In the EMA biosimilar guidances that have been issued for other classes of proteins, no non-clinical PK studies are recommended. PK information in animals is of limited value; however, drug exposure (concentration) data should be collected from the toxicology study only for the purposes of assisting the interpretation of the toxicology data. We suggest that a similar approach be taken for this biosimilar guidance.	Agreed, sentence added to highlight this point. Please see previous comments and also discussions in the non-clinical sections.
22	Issues Missing from the Guideline We feel the Guideline is missing clarity on expected implications for summary of product characteristics (SmPCs) for monoclonal antibodies – clarity of the status of data extrapolated or not is especially important. The Guideline does not address the clinical picture in which the	Please see comments elsewhere in this document.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	biosimilar will be approved: should a higher standard of physiochemical and biological similarity be imposed for therapies where the innovator demonstrates a complete cure vs. therapies with only mitigating effects? BIO appreciates this opportunity to comment on "Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies." BIO provided specific comments on sections of the draft guidance in Section 2. In the left column of the table, we identify the line number in the draft guidance; the middle column contains BIO's comments and rationale to support our position and carries our suggested changes, where applicable (single strikeout for deleted text and bold, underlined type for added text). We would be pleased to provide further input or clarification of our comments, as needed	

2. Specific comments on text

GENERAL REMARK: The comments made on the Executive Summary will not be commented on (unless felt necessary), since there will be comments in the specific sections of this document on these items again. The Executive Summary was updated accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
39	20	Comment: The guideline does not cover CMC comparability however there should be text linking the sequential establishment of the product being "highly similar" through each level of assessment. Proposed change: "This guideline lays down the non-clinical and clinical requirements for monoclonal antibody (mAb). The assumption is made that a high level of similarity will also be established using 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. More information on the selection of analytical and *in vitro* tests is required and this information should be disclosed prior to the finalisation of the draft guidance.	A wording similar to this one has been included in the updated guideline. Please see comments elsewhere in this document (reference to guideline on quality control of mAbs).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
39-40	17	Comment: It is stated here that a biosimilar product is claiming to be similar to another one already "marketed". In reference to Directive 2001/83/EC as amended it should read "…to another one already **authorised".** **Please refer also to comment regarding line 195.** Proposed change: Change sentence to read: "….products claiming to be similar to another one already ~~marketed~~ **authorised."**	Proposal accepted.
40	20	Comment: "…products claiming to be similar to another one already marketed." It should be clarified that the reference product needs to be authorised in the EU market and this sentence should be modified, accordingly, to communicate whether or not a product that is marketed outside the EU (but not in the EU) could be used as a reference product. Proposed change: Please change to "…already marketed in the EU"	This is not restricted to mAbs, and is therefore not included in the guideline. Please refer to the general guideline on biosimilars.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
40	21	**Comment:** "..products claiming to be similar to another one already marketed." Since the reference product needs to be authorised in the EU, this sentence should be modified not to give the impression that a product that is marketed outside the EU (but not in the EU) could be used as a reference product. **Proposed change (if any):** Please change to "..already marketed in the EU"	This is an identical comment to above, Please see previous comment.
44-45	20	Comment: The recommended risk-based and case-by-case approach does not provide sufficient directions for decision making on the extent of non-clinical studies. Proposed change: Please clarify what data are viewed as being ideal for making the case-by-case determination, especially as it relates to the need for *in vivo* studies.	Non-clinical section has been rediscussed to reflect the current thinking of the CHMP. For a more general guideline on biosimilar mAbs, it has now the level of what can be recommended on such basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
46	11	Proposed change (if any): For clarity, "non-clinical" should be added after *in vivo* to make clear that it applies to *in vivo* non-clinical studies.	Agreed – this has been put in guideline text
Lines 46-47, 127-128	21	**Comment:** ."..a decision then made as to the extent of what, **if any**, *in vivo* work will be required." Please refer also to our General comments on Nonclinical Studies regarding this comment. The biosimilar manufacturer does not have sufficient data as the innovator has generated over years to set acceptance criteria on all key quality attributes, and many important attributes are not well understood. Post-translational modifications may have *in vivo* effects on biodistribution/PK, binding and effector function. Given the unknowns, particularly with off target toxicities, it is not recommended to go directly from *in vitro* studies to a clinical study. Therefore we find the current wording "if any" and "if needed necessary" inappropriate. For support of safe first-in-man trials with a mAb biosimilar, the association of *in vitro* functional properties and any consequences on the in-vivo PK/PD/safety relationship should be assessed <u>in at least</u>	Not accepted. Please see previous comments on the need for toxicology studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		one clinically relevant animal study. The use of alternative models/approaches to studies in non-human primates should be considered if scientifically justified. This is in agreement with the existing EMA regulatory guidance on biosimilars. There is yet no or very limited *in vivo* experience with biosimilar mAbs; it is therefore advisable to be cautious at the beginning of this process while once there is experience with certain mAbs classes, the use of non-clinical safety studies may become less important. **Proposed change (if any):** For support of safe first-in-man (FIM) trials with biosimilar mAbs, the association of *in vitro* functional properties and any consequences on the in vivo PK/PD/safety relationship should be assessed in at least one clinical relevant animal study. The use of alternative models/approaches to studies in non-human primates should be considered if scientifically justified.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
46-49	7	Comment: It is stated that "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 current wording "if any" and "if …deemed necessary" is not supported in light of industry experience to date. We recommend that at least one *in vivo* animal (PK/PD/safety) study should be the default requirement prior to first-in-human trials with biosimilar monoclonal antibodies (mAbs).	Not accepted, Please see explanations elsewhere.
46-49	20	Comment: "…a decision then made as to the extent of what, if any, *in vivo* work will be required." We find the current wording "if any" and "if …deemed necessary" not supported by the industry experience to date. We recommend that at least one animal *in vivo* (PK/PD/safety) study should be the default requirement prior to First-In-Human administration. Proposed change: For support of safe first-in-human (FIH) trials with biosimilar mAbs, the association of *in vitro* functional properties and any consequences on the *in vivo* PK/PD/safety relationship should be assessed in at least one clinically relevant animal study. The use of alternative models/approaches to studies in non-human primates should be considered if scientifically justified.	Not accepted, Please see explanations elsewhere.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47-49	17	Comment: Non-clinical studies for biosimilar products should typically be comparative unless otherwise justified because it is not the pharmacological profile as such which is investigated, but the comparison to the reference product. Proposed change: To replace the word "normally" by "typically unless otherwise justified": "If an *in vivo* study is deemed necessary, the focus of the study (pharmacokinetics, pharmacodynamics, and/or safety; ~~normally~~ **typically** comparative in nature **unless otherwise justified**) depends on the need for additional information, and the availability of a relevant animal model."…	Partly accepted. The paragraph has been changed.
49	21	**Comment: "**The conduct of large comparative toxicological studies in non-human primates is not recommended." Particularly when there is a narrow therapeutic index, a nonclinical comparative study will be essential to minimize risk to clinical population. Small differences in tertiary structure have sometimes resulted in unexpected changes in toxicity profiles. *In vitro* testing alone cannot identify all changes in risk. **Proposed change (if any):):** State that comparative	Not accepted. Small changes in PD are expected, however unexpected changes in toxicity profiles are not anticipated and thus do not need to be examined in a comparative way.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in vivo safety assessment is required, not optional	
49-50	20	Comment: "The conduct of large comparative toxicological studies in non-human primates is not recommended." *Large* comparative studies may not be needed (see proposals to reduce dose levels, one gender, no recovery groups case-by-case). If a high degree of similarity in quality characteristics and functional *in vitro* studies between the reference and biosimilar products is demonstrated, only PK/PD experiments (e.g., with some safety endpoint evaluation) may be sufficient. If NHP is the only appropriate species, then it may still be necessary to undertake this study. Studies should be relevant, as efficient as possible and scientifically justified. The default should be the conduct of at least one animal PK/PD/safety study to support FIH administration. Proposed change: The conduct of large comparative toxicological studies in non-human primates is not recommended, however, at least one comparative *in vivo* PK/PD/safety assessment study in relevant species is required.	Not accepted. Please see comments elsewhere in this document on the need for toxicology studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
50-59	20	Comment: The emphasis here is on PK studies however, those cannot be expected to show substantial differences since all MAbs - being IgGs - are expected to have similar kinetics. The critical issues in establishing biosimilarity are the specificity, potency and biologic effect of the new molecule as well as its immunogenic potential compared to its predecessor. Proposed change: Consider revising based on key differences in the aspects critical to large molecule development rather than suggest small molecule strategies which will not be fully informative	This comment is not agreed. Substantial differences have been seen even with a given mAb between several clinical indications. This may not be problematic for a biosimilar scenario (depending on supportive data, scientific justification, overall dataset etc.), but it mandates that the emphasis on PK studies should currently remain.
52	20	Comment: Generally it might be helpful if the guideline were more consistent with terminology, such as "biosimilar = similar biological", "reference product = reference medicinal product", etc. Proposed change: Modify the text already here, e.g. "biosimilar (similar biological medicinal product)…", and use term "biosimilar" in the following text?	Agreed. Terminology has been made consistent.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52	21	**Comment:** Generally it might be helpful if the guideline were more consistent with terminology, such as "biosimilar = similar biological", "reference product = reference medicinal product", etc. **Proposed change (if any):** Modify the text already here, e.g. "biosimilar (similar biological medicinal product)..", and use term "biosimilar" in the following text?	Please see above.
53	17	Comment: This sentence very much reduces the choice of PK design which is not scientifically justified. Therefore, we propose to delete the word "usually" Proposed change: Replace "usually" by "for example": "….normally forms an integral part of biosimilar mAbs development, ~~usually~~ **for example** in a parallel group design due to the long half-life of mAbs and potential interference of immunogenicity."	BMWP prefers the previous version with "usually", since one would rather expect a parallel group design for the reasons explained in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
54-55	20	Comment: The design of a pharmacokinetic study should also account for variability in "antigen load" for example in oncology settings where the target antigen is associated with the tumour and is thus impacted by "tumour load". Proposed change: The design of a pharmacokinetic study will depend on various factors, including clinical context, linear versus non-linear pharmacokinetics, **confounding disease characteristics (e.g. "tumour load" and thus "antigen load" in an oncology setting)** etc	Is reflected in the main guideline text, chapter 5.1. The Executive Summary should at best not be further extended (Please see comments requesting shortening).
56-59	21	**Comment:** Pharmacokinetic assessment during clinical efficacy studies or the conduct of multiple-dose pharmacokinetic studies is recommended only on a case-by-case basis. It appears to be difficult to establish efficacy and safety without a concomitant assessment of exposure to the mAb as a standard requirement. **Proposed change (if any):** Pharmacokinetic assessment should be included in clinical efficacy studies to allow correlation of efficacy and safety with exposure to the mAb (i.e.: exposure-response assessment).	Please see specific comments for chapter 5.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
56-59	20	Comment: The draft guidance on lines 56-59 recommends that pharmacokinetic assessment during clinical efficacy studies or the conduct of multiple-dose pharmacokinetic studies are to be conducted only on a case-by-case basis to establish similar efficacy and safety. Monoclonal Ab pharmacokinetics can change after repeated administration, so obtaining multiple pharmacokinetic data is essential to establishing biosimilarity. Immunogenicity that develops after repeated administration can increase mAb clearance. The development of ADA can be different between a biosimilar and innovator and thus multiple dose studies should be required. A population PK/PD analysis conducted with data from a clinical efficacy study is a valuable approach for obtaining these data. It would be difficult to establish efficacy and safety without a concomitant assessment of exposure to the mAb as a standard requirement from these types of studies Proposed change: ~~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. Obtaining multiple dose pharmacokinetics is important	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for establishing biosimilarity. Pharmacokinetic assessment should be included in clinical efficacy studies to allow correlation of efficacy and safety with exposure to the mAb (i.e. exposure-response assessment).	
60-62	7	Comment: It is stated that sponsors should "explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity". This approach is valid for those biologics, such as cytokines, that are approved for use at multiple or variable doses, when these doses lie on a reasonably steep portion of the dose-response curve, and for which a sensitive pharmacodynamic (PD) marker is available. It is noted that most approved antibodies are highly targeted therapies that are generally used and approved at or near the top of their dose-response curve; many also do not have sensitive PD markers. We believe it would be inappropriate (and often clinically unfeasible) to study reference product antibodies at doses other than those that are approved. Proposed change: "For those products approved at multiple doses and used at doses on a reasonably sloped segment of their	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dose-concentration-response curve, ~~S~~sponsors should always explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity."	
60-62	15	Comment: The draft text states that sponsors should "explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity." This approach is valid for those biologics, such as cytokines, that are approved for use at multiple or variable doses, when these doses lie on a reasonably steep portion of the dose-response curve, and for which a sensitive pharmacodynamic (PD) marker is available. We note, however, that most approved antibodies are highly targeted therapies that are generally used and approved at or near the top of their dose-response curve; many also do not have sensitive PD markers. We, therefore, believe it would be inappropriate (and often clinically infeasible) to study reference product antibodies at doses other than those that are approved. Proposed change: ***"For those products approved at multiple doses and used at doses on a reasonably sloped***	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		segment of their dose-concentration-response curve, ~~S~~***s***ponsors should explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity."*	
60-62	20	Comment: The draft text states that Sponsors should "*explore possibilities to study dose-concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity.*" This approach is valid for those biologics, such as cytokines, that are approved for use at multiple or variable doses, when these doses lie on a reasonably steep portion of the dose-response curve, and for which a sensitive pharmacodynamic (PD) marker is available. We note, however, that most approved antibodies are highly targeted therapies that are generally used and approved at or near the top of their dose-response curve; many also do not have sensitive PD markers. We believe it would be inappropriate (and often clinically infeasible) to study reference product antibodies at doses other than those that are approved. Proposed change: "For those products approved at multiple doses and used at doses on a reasonably sloped segment of their	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dose-concentration-response curve, sponsors should explore possibilities to study dose -concentration-response relationships since this approach, if successful, may provide strong evidence of biosimilarity.”	
62-64	17	Comment: The design of the clinical trial to establish similar clinical efficacy very much depends on the nature of the disease to be investigated. Usually, a non-inferiority design to demonstrate that the test product is not worse than the reference product has been widely accepted when comparing a new treatment vs. the standard of care. However, for demonstration of biosimilarity, in some indications where the therapeutic margin is clearly defined, an equivalence design may be preferred (e.g. diabetes). But for some indications like oncology, a non-inferiority design seems acceptable as a slightly higher efficacy with comparable safety would be acceptable. This could lead to further reduction of the study sample size. Proposed change: Normally, similar clinical efficacy should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, ~~normally~~ **typically** equivalence **or, if appropriately justified, also non-inferiority** trials.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
62-73	11	Comment: It seems difficult to propose that PK-PD could be sufficient without a very tight link between the PD and the usual clinical endpoint. It seems that at least one clinical trial should be required, unless such a strong link can be established for PD to the clinical endpoint. Proposed change (if any): Suggest adding "At minimum, clinical investigation in one sensitive or representative population, with sensitive endpoints or biomarkers for equivalence or efficacy determination, should normally be required unless a strong link between PD and clinical outcomes can be established."	Please see specific comments for the main guideline text.
62-73	20	Comment: It is difficult to propose that PK-PD could be sufficient without a very tight link between the PD and the usual clinical endpoint. At least one clinical trial should be required, unless such a strong link can be established for PD to the clinical endpoint. Proposed change: "clinical studies in at least one sensitive population are normally required unless a strong link between PD and clinical outcomes can be established"	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
63-64	11	Comment: We would appreciate more detailed guidance on "normally equivalence trials". It has not been unusual that drug performance falls outside very tight equivalence margins numerically and/or statistically, but such difference is not clinically relevant. Therefore, there is a strong need for the guidance document to establish clinically relevant definitions of equivalence which would account for the concern discussed above.	Please see specific comments for the main guideline text.
63-64	20	Comment: Equivalence trials should be the standard. Proposed change: "Normally, similar clinical efficacy between the biosimilar and reference product should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double blind and usually an equivalence trial. PK/PD similarity does not always translate into efficacy and safety similarity. It is not uncommon that a "highly sensitive" PD marker is not "clinically relevant". If a validated surrogate PD endpoint is available (eg: BP drop, HbA1c), then they provide confidence related to clinical outcome. In such cases, similarity can be partially assessed based on that PD endpoint. Only in the case that a PD marker is a validated and recognized regulatory endpoint for the approval of a product in the studied indication can it be used for the primary	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		evaluation of similarity.”	
64	20	Comment: Deviations from disease-specific guidelines issued by the CHMP (for example, choice of endpoint, time point of analysis of endpoint, nature or dose of concomitant therapy) may be warranted. However the surrogate should be scientifically valid and should be justified on the basis of the target, potential adverse events/immunogenicity etc Proposed change: “Disease-specific guidelines should, in principle, be followed to assure similarity and provide an adequate test of comparative safety. However, to establish biosimilarity, deviations from these guidelines (choice of endpoint, time point of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. To establish biosimilarity the primary endpoint chosen should always be contingent on there being a validated, scientifically acceptable and regulatory accepted endpoint for a product being developed for the studied indication.”	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
64-66	10	Comment: The sentence implies that deviations from disease specific guidelines may be warranted, we recommend further clarification of the circumstances for deviating from the guidelines should be provided. For example by specifying that, under such circumstances whereupon deviations from disease-specific guidelines occur, they must be strongly justified with data from both the scientific literature and clinical studies, that demonstrate the newly proposed endpoints have indeed been previously validated through well and adequately-controlled clinical studies and disease area specific consensus guidelines.	Please see specific comments for the main guideline text.
65-66	2	Comment: That a deviation from guideline may be warranted is not really helpful advice in a guideline. Equivalence can only be demonstrated with efficacy endpoints of the reference product used as primary or secondary endpoints according to guidelines. Proposed change (if any): Delete 65-66 (to establish….be warranted.	Not accepted, Please see argumentation in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
64-66	22	**Comment:** Disease-specific guidelines should, in principle, be followed to assure similarity and provide an adequate test of comparative safety. In deviating from guidelines, the safety in relation to duration of treatment/clinical observation time cannot be adequately assessed unless it is clear that the duration of observation is adequate for nearly all critical safety findings, including immunogenicity, to be observed. We suggest that study designs include endpoints which allow for sufficient durations of treatment to permit evaluation of safety/immunogenicity and its relationship to efficacy. **Proposed Change**: "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.~~ **However, the study designs should include endpoints which allow for sufficient durations of treatment to permit evaluation of safety/immunogenicity and its relationship to efficacy.**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
66-68	20	Comment: *"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."* Without some relationship to patient benefit, these would be merely PD studies in the target population and not allow for benefit risk modelling. In particular, a focus on PD endpoints will not necessarily allow the impact of differences in quality attributes on the safety/immunogenicity profile to be observed. Suggest it be mandated that duration of treatment be sufficient to permit observation of mechanism-based and other adverse experiences, immunogenicity, and, in passing (relative to safety outcomes), to achieve similarity of a meaningful clinical endpoint relatively not only to PD, but also efficacy. Sample size should be sufficient to demonstrate an estimate of treatment effect with a confidence bound sufficient to avoid conclusion of no treatment difference when one actually exists.	Please see specific comments for the main guideline text.
68-70	20	Comment: We recommend that the most sensitive model should also be explicitly stated to also be an approved indication for the reference product and that a different approach should be thoroughly justified.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
68-73	20	Comment: If the pivotal study population is too narrowly defined and hence very homogeneous, caution should be used to extrapolate clinical efficacy and safety to other indications by the population being treated. If PD can prove similarity for efficacy, then more guidance is needed on what is necessary to prove similarity for safety.	Please see specific comments for the main guideline text.
69	20	Comment: "*homogeneous population*" - This is difficult to define, no less achieve. In oncology indication, genetic background, total tumor burden and other factors make it difficult to have a truly homogeneous population.	Please see specific comments for the main guideline text.
70-73	20	Comment: There are no validated PD markers that translate into efficacy or safety of the product. Neither CRP nor rheumatoid factor are appropriate.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
72-75	2	Comment: Measure and equivalence margin placed in connection. Proposed change (if any): Applicants will have to choose clinically relevant markers and 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 efficacy, safety and immunogenicity are covered.	Please see specific comments for the main guideline text.
73-77	20	Comment: The agency should provide very specific guidance around what equivalence margins are needed - which should be the 80-125 equivalence margins.	Please see specific comments for the main guideline text.
76-77	2	Comment: Comparable safety as a measure of biosimilarity is not feasible without a large database. Proposed change (if any): 76-77 ".. Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity." should be deleted.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
76-77	5	Comment: We agree that a comparison of pharmacologically mediated adverse events is relevant to the assessment of biosimilarity. We suggest recasting the point as an observation that a difference with respect to this measurement will *prevent* a finding of biosimilarity. Proposed change (if any): ~~"Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity.~~ **Because pharmacologically mediated adverse events reflect the activity of the biological in question, differences between the proposed biosimilar and reference product with respect to pharmacologically mediated adverse events will prevent a finding of biosimilarity."**	Please see specific comments for the main guideline text.
76-77	15	Comment: The draft text indicates that comparable safety with respect to adverse reactions could also be considered a measure of biosimilarity. This text does not consider the developments in manufacturing process knowledge and expertise that have occurred – which can permit the development of a biosimilar monoclonal antibody which might result in a lower incidence of adverse reactions, due to increased process understanding and techniques.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The guidance should reflect that adverse reactions should be expected to be at least comparable.	
76-77	20	Comment: MAb biosimilar applicants should be required to demonstrate that the products have similar adverse event profiles (in terms of incidence, type, and severity of events). A product with a different adverse event profile, even if seemingly improved, might be deemed not biosimilar because the product would have been proven to be different. Moreover, all of the implications of that difference may not be apparent without a full development program. Proposed change: "Differences in safety with respect to pharmacologically mediated adverse reactions will prevent a finding of biosimilarity." Comment: "*Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity*." If this sentence describes the intent of a study endpoint, then further clarity should be provided on expectations as it is not clear how only assessing safety and not efficacy can be used	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to establish similarity.	
76-77	22	**Comment:** The Guideline states, "Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity." **Proposed Change:** If this sentence describes the intent of a study endpoint, then we ask that further clarity be provided on expectations.	Please see specific comments for the main guideline text.
77	21	**Comment:** "Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity"' It would be good to stress that e.g. this parameter would, however, not be adequate alone to demonstrate biosimilarity. In addition, the biosimilar or reference product is not always the actual root cause of all the adverse reactions detected. **Proposed change (if any):**	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
77-79	21	**Comment: "**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…." This gives the impression that extrapolation is always possible, therefore recommend rewording **Proposed change (if any): "**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, may be possible based on the results of the overall evidence provided. The burden to extrapolation across indication should be tailored to the benefit brought by the reference product and customized for each indication, specially where cure is the expected treatment outcome	Please see specific comments for the main guideline text.
77-79	20	Comment: **"***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….*" This gives the impression that extrapolation is always possible, therefore recommend rewording.	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "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~~ may be possible based on ~~the results of the overall evidence provided from~~ the biosimilarity exercise ~~and~~ with adequate justification, which should include consideration on differences in posology, mechanism of action (or uncertainty around mechanism of action), distinct safety profiles between indications, and the different combination agents in different diseases as the AE profiles may not be directly extrapolated due to a different pharmacodynamic interaction with the different combination agents. The burden to extrapolation across indication should be tailored to the benefit brought by the reference product and customized for each indication, especially where cure is the expected treatment outcome. Possible safety issues in different subpopulations should also be addressed."	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
77 – 80 425-428	6	Comment: "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." Proposed change (if any): "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~~ may be possible based on the results of the overall evidence provided from the biosimilarity exercise and with adequate justification." Comments: • The guidance should reiterate the criteria for extrapolation outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues". It should also emphasize that possible safety issues in different subpopulations should be evaluated in clinical trials. • For those biopharmaceuticals where the mechanism of action is comprehensively understood, extrapolation may be feasible on the basis outlined in the above mentioned	Not agreed, Please see explanations elsewhere in this document (repetitive comment). Briefly, reiteration of issues from another guideline, especially general guidelines, is superfluous, and the reader should rather refer to those guidelines individually. As regards extrapolation, some arguments are rather relevant for a new-in-class rather than a head-to-head comparison of a biosimilar mAb with a reference mAb in a biosimilarity exercise, e.g. different pathogenesis etc.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		general guidance. However, for mAbs, where the mechanism of action is rather complex and often only partially understood, a more cautious approach regarding extrapolation should be taken. • Example autoimmune diseases: In spite of sharing some common pathogenetic mechanisms, different autoimmune diseases can vary significantly in e.g. target organ(s), clinical manifestations, time of onset, prognosis, speed of progression, gender prevalence, etc. As a result, response to immunomodulators even with identical mechanism of action and PD is extremely variable. • Extrapolation of safety also poses risks because the safety profile of immunomodulators across the different diseases can vary even within the same molecule. • In general, extrapolation of indications requires well-balanced assessments and might not be possible in many cases. To mitigate risks associated with extrapolation of indications, similarity should be demonstrated in the indication where the treatment with reference product provides the best outcome (e.g. OS). • If similarity is established in the appropriate indication, extrapolation to other indications may be granted in case of proper justification	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(e.g. high degree of molecular similarity, same expression system, same mode of action, same drivers of PK, validated in vivo PD surrogates, etc.).	
77-80 425-428	15	Comment: As regards to the extrapolation of clinical efficacy and safety data to other indications of the reference mAb, it could be useful to consider the EMA non-clinical and clinical general biosimilar guideline issued on 2006 February 22, where it is underlined that "the efficacy and safety of the medical product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications" Moreover, there could be different safety issues within the subpopulations, and therefore this needs to be addressed. Proposed change: "***In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed***	Not agreed, Please see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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~~ ***may be*** possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification."	
80-82	7	Comment: It is stated "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." It is suggested that until sufficient experience is achieved with biosimilars and comparative predictive immunology, active pharmacovigilance should be required to provide insight into unexpected safety signals, including evidence of anti-drug and neutralizing antibodies. Proposed Change: We suggest adding: "**Active pharmacovigilance measures covered in the risk management plan should include assessment of adverse events that were not fully evaluated in the pre-authorisation period, and, if necessary, active surveillance for the incidence and impact of anti-drug antibodies.**"	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
80-82	17	Comment: Biosimilar products will have been extensively characterised showing no meaningful differences in comparison to the reference product and comparable efficacy and safety. Therefore, the pharmacovigilance rules applicable to biological products should be the same for biosimilar products. It is not clear what is meant by "more standardized environments". We suggest clarifying by referring to the implementing measures of the new EU PhV legislation. Proposed change: 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~~ **should follow the same pharmacovigilance rules as applicable to any biological product and take into account pharmacovigilance guidelines and measures following the implementation of the new EU Pharmacovigilance legislation.**	Please see specific comments for the main guideline text.
80-82	22	**Comment:** The Guideline states, "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."	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We suggest that until sufficient experience is achieved with the biosimilar, active methods of pharmacovigilance should be required to provide the best chance for observation of unexpected safety signals, including evidence of neutralizing antibodies, allowing for the possibility that unique attributes of the biosimilar and/or its formulation may predispose to the formation of antibodies in patients, including patients previously exposed to innovator product. **Proposed Change:** We suggest strengthening the requirement for active pharmacovigilance measures. Additional text could include, "**Active pharmacovigilance measures covered in the risk management plan could include labeling notifications to ensure traceability of adverse events to the manufacturer, tracking of adverse events that were not fully evaluated in the pre-licensing period, and, if necessary, active surveillance for the incidence and impact of anti-drug antibodies.**"	
80-82	21	**Comment:** It would be good to stress the need for proper identification of biologics to ensure traceability also in this guideline	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
81	11	Comment: The guidance needs to clarify the term of "routine pharmacovigilance". Applicant should go beyond "routine pharmacovigilance" specifically to address the potential for immunogenicity to be routinely assessed in the post-market environment, since this remains one of the most important unanswered longer-term safety issues. The guidance also needs to specify the need for capturing more post-marketing data on "unstudied", extrapolated indications. Proposed change (if any): "Applicant may have a need to go beyond routine pharmacovigilance to include, amongst other things, assessing immunogenicity in the post-market environment and for "unstudied", extrapolated indications".	Please see specific comments for the main guideline text.
81	20	Comment: "*Applicants may have to exceed routine pharmacovigilance*" should be extended to specifically address the potential for immunogenicity to be routinely assessed in the post market environment, since this	Please see specific comments for the main guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		remains one of the most important unanswered longer term safety issues. Proposed change: "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." Until sufficient experience is achieved with the biosimilar, active methods of pharmacovigilance should be required to provide the best chance for observation of unexpected safety signals, including evidence of neutralizing antibodies, allowing for the possibility that unique attributes of the biosimilar and/or its formulation may predispose to the formation of antibodies in patients previously exposed to innovator product.	
88	21	**Comment: "**Each individual mAb may present a unique profile with respect to the criticality of the 90 antigen-binding region, the Fc cytotoxic effector function, and binding to Fc receptors including FcRn." **Proposed change (if any):** Please modify to: "Each individual mAb presents 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."	Agreed, text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
93	21	**Comment:** "…be difficult to conclude on the…." Incorrect word used here. **Proposed change (if any):** Replace "conclude on" with "interpret."	Agreed, word changed.
84-98	20	Comment: It is not clear that the "Introduction" section is referring to biosimilar mAbs. Recommend rewording to clarify issues that are specific to biosimilar monoclonal antibodies. Proposed change: Monoclonal antibodies (mAbs) 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~~Mabs are structurally complex glycoproteins, and may have several functional domains within a single molecule,	Partly agreed, some suggestions taken into the text. Some deletions were not accepted where BMWP felt the text important.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~depending on the isotype~~ (antigen-binding region, complement-binding region, constant part interacting with Fc receptors). Each individual mAb ~~may~~ presents 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,~~Although various assays have been established ~~in the past years~~ that allow for more in-depth characterization 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 make conclusions on the relevance of minor quality differences in the physicochemical and biological characterization of a similar and a reference mAb. 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).	
92-94	21	**Comment:** "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…" Wording suggests that it is not possible to know which measurable structural changes in a mAb are	Agreed, text has been made clearer. It was meant only to discuss the pro's and con's, but not to conclude if physicochemical and biological characterization is sufficient or not. This will depend on the methods applied, the mAb in question etc

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		relevant/impactful on safety/efficacy. The majority of this paragraph argues against analytical techniques being sufficient to declare "similarity". However, this conclusion could be made more clear if it is one of the main rationales for the guidance, add e.g. : ", and therefore appropriate, comparative human and animal data, in addition to comparison at quality level are normally needed..." **Proposed change (if any):** Please consider revision	
92-94	20	Comment: "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…" Wording acknowledges the difficulty in the interpretation of analytical data showing minor structural differences in mAb therapeutics and whether or not these differences are relevant to safety/efficacy. The paragraph implies that analytical techniques are not sufficient to declare "similarity". However, this conclusion could be made clearer and be used as the main rationale for requesting appropriate *in vivo* comparative (animal and human) data in addition to	Please see similar comment before.

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		comparison at quality level. Proposed change: Please consider revisions.	
93-94	7	Comment: It is stated "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". Proposed change: We suggest adding: "Clinical studies providing comparable safety and efficacy are required, until such time as this knowledge exists."	Please see similar comments before.
93-96	22	**Comment:** The Guidance states "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." We suggest that the statement should provide a clear consequence of these limitations. **Proposed Change:** "However, it may at the current stage of knowledge be difficult to conclude on the relevance of minor quality differences in the	Please see similar comments before.

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		physicochemical and biological characterization. **Until such time as this knowledge exists, clinical studies of comparable safety and efficacy are required.**"	
95-96	17	Comment: The wording of this sentence starting with "Nevertheless…" is very suggestive. One might get the impression that CHMP considers the development of mAbs a hopeless endeavour. Moreover, it is not clear what is meant by such antibodies- complex or *biosimilar* antibodies? Furthermore, CHMP has experience in evaluating minor quality differences due to manufacturing changes of originator mAbs. Also it is not clear what is meant by "some individual products" – *originator* or *biosimilar* products? Proposed change: Please do not restrict to biosimilars and rephrase the sentence as follows: **"Nevertheless, the CHMP has experience in evaluating minor quality differences due to manufacturing changes of originator mAbs and has given scientific advice for the development of some individual products."**	Agreed, Please see also comments above. This paragraph was apparently confusing and has therefore been revised.

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99	20	Comment: **"**For quality aspects the principles as laid out in the comparability guidelines including the "Guideline on.." Additional clarification on applicability of the "comparability" guidelines to "biosimilar" guidelines is warranted. Proposed change: **"**For quality aspects the principles as laid out in the biosimilar guidelines including the "Guideline on.."	Agreed, has been changed for the final draft.
99	21	**Comment: "**For quality aspects the principles as laid out in the comparability guidelines including the "Guideline on.." Incorrect/confusing wording here, these are not "comparability" guidelines but biosimilar guidelines. **Proposed change (if any): "**For quality aspects the principles as laid out in the biosimilar guidelines including the "Guideline on.."	Please see above.
106-119	15	Comment: Conjugated monoclonal antibodies and radio-labelled antibodies should be explicitly excluded from the scope of the guidance.	BMWP acknowledges that conjugated mAb products have an added complexity as compared to non-conjugated mAbs. However, since the guideline does not involve discussions around structural complexity, the BMWP prefers to not

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		We note that there is a growing class of combination products that have a critical biological component but whose primary mode of action requires a non-biological (small molecule or peptide) component. Such products are often referred to as drug-antibody conjugates or conjugated antibodies. Our view that such products should be excluded from the scope of this guidance at this time is based on the structural, pharmacological, biological, and medical complexity of these products. <u>Rationale</u> First, with regards to structural complexities, such products not only raise the same structural, manufacturing, and characterization complexities as antibody products, but also involve very complex chemical conjugation technology and are subject to variable rates and locations of chemical modification; this adds an additional layer of variability on top of the variability already inherent in the antibody portion of these molecules. Specifically, these products start with a range of structures in the antibody sub-component, and then variably chemically modify this range of structures. These products also normally require specialized analytical characterization techniques that are very unlikely to be reproducible to the necessary degree by a biosimilar product developer. This latter factor is in contrast to unconjugated antibodies: while the analytical techniques required to confirm a high level of similarity between unconjugated antibodies may	explicitly mention this product subclass at this time.

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		be complex, they are available to a range of companies and are often not highly customized. Further, the extent and location of conjugation of the chemical moieties in antibody-drug conjugates is highly critical to the pharmacology and safety of these products, and the extent and location of conjugation is highly dependent on the manufacturing process. Second, as to pharmacological and biological complexity, conjugated antibodies often rely on a highly specific interaction with a cell surface target to achieve internalization of a highly toxic chemical moiety into specific cell types and cellular compartments, where the toxin is then released and has its activity. This internalization process involves a very complicated cellular and molecular choreography, and this choreography is highly critical to the pharmacology and safety of these molecules. In order for a biosimilar version of such a molecule to be developed, it would be necessary for in vitro cellular characterization methods to be available to confirm a high level of similarity in this regard, and it would be important for the reference product and biosimilar product in vitro methods to be shown to be equivalent. Showing such analytical method equivalence will generally not be feasible given the specialized and highly customized nature of such test methods. Third, regarding medical complexity, such products are often for medically critical diseases, such as refractory oncology populations.	

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		Radio-labelled antibodies are similarly complex and the same approach should be taken Proposed change: The final guidance should state that conjugated antibodies and radio-labelled antibodies, given their additional complexity, are excluded from the scope of the guidance at this time.	
107-115	7	Comment: Whilst described as "product specific guidance" we believe it would be more appropriate to present the guideline as 'class' specific with some further specific class and product types elucidated directly within this guideline or separately. It is suggested that, given their additional complexity, conjugated antibodies and radio-labelled antibodies are excluded from the scope of the guideline at this time. It would be helpful if examples of biologicals that are considered "structurally altered" are provided for clarity. It is recommended that the guideline clearly states that the biosimilar product must at a minimum have the same amino acid sequence as the reference product.	Partly agreed, text has been modified for the final draft proposal as regards the word "product specific guidance" and as regards "structurally altered" mAbs. As regards product-specific guidance and the other aspects, please refer to responses to similar comments elsewhere in this document.
109	20	Comment: In our view a biosimilar should be as similar as possible to the reference product not only in terms of safety and	Please see response to similar comments elsewhere in this document.

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		efficacy but also in terms of structure and identical amino acid sequence. In addition, we do not regard this guideline as a "product specific guideline" since it intends to cover all mAb products. Proposed change: Add a requirement that as a principle biosimilars must have the same amino acid sequence(s) as the reference molecule, and that only unintended differences e.g. in post-translational modifications could be justified.	
109 ff	21	**Comment:** It has to be better specified that a biosimilar should be as similar as possible to the reference product not only in terms of safety and efficacy but also in terms of structure and sequence. In addition, as mentioned in the general comments above, we do not regard this as a "product specific guideline" since it intends to cover all mAb products. **Proposed change (if any):** **Add a requirement that as a principle biosimilars must have the same amino acid sequence(s) as the reference molecule**, and that only unintended differences e.g. in post-translational modifications could be justified.	Please see response to similar comments elsewhere in this document.

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115-117	15	Comment: The draft document states that, "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." Proposed change: For clarity, it would be useful if examples of biologicals that are considered "structurally altered" are provided in the final guideline.	Please see response to similar comments above.
115-118	7	Comment: It is stated "Second- or next-generation biologicals … are beyond the scope of this guideline. Nevertheless, principles laid down in this guideline could apply on a case-by-case basis." It is suggested that this concept may be more appropriately described in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (overarching guideline) as it may not be restricted to mAbs. Further discussion of the limits of differentiated biologicals claiming similarity for the purposes of abbreviated evaluation would be helpful for	Agreed, text has therefore been changed from "biologicals" to "mAbs".

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		sponsors. It is recommended that the scope of the guideline should be limited to mAbs claiming similarity to an already authorised product.	
115-119	1	Comment: Here an abridged procedure is suggested for biobetters. Is there an initiative at the EMA/CHMP level to come with a new procedure for biobetters? Proposed change (if any): Take out the sentence "Nevertheless, principles laid down in this guideline could apply on a case-by case basis." in order not to open the door for biobetters based on this guideline.	BMWP disagrees, since some aspects may be relevant. Nevertheless, the guideline remains silent about "biobetters".
115 - 119	4	Comment: Here an abridged procedure is suggested for biobetters. Is there an initiative at the EMA/CHMP level to come with a new procedure for biobetters. Maybe we can suggest to write a white paper on the immunogenicity issues of biobetters?	Please see comments above. Suggestion for "biobetters" noted.
115 - 119	5	Comment: We agree that second- or next-generation biologicals are beyond the scope of the guideline. The subsequent sentences — that the principles laid down in the guideline "could apply on a case-by-case basis" and	Please see comments above.

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		that sponsors of those products should seek scientific advice — are unnecessary and may lead to confusion. The principles set forth in the draft guideline will be of little relevance to these products, because these products are not authorized on the basis of abbreviated, comparative non-clinical and clinical programs. We suggest these sentences be deleted. Proposed change (if any): "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."~~	
115-119	22	**Comment:** It is unclear why this mAb guideline should mention the topic of structurally-altered biologics. This is a general topic and was not addressed in existing CHMP guidelines. It is out of place to mention it in a non-clinical and clinical guideline specific to mAbs. Indeed, the premise appears incorrect that any concepts contained in this Guideline could apply to such a situation since there would be no premise that the products should have the same pharmacology or pharmacokinetics. Such structurally altered products	Please see comments above.

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		should only be approved on the basis of full data sets showing safety and efficacy in each condition of use. **Proposed Change:** We suggest the mention of structurally-altered biologics (lines 115-119) be removed or that the text stop at line 117, concluding that such biologics are out of scope.	
120	10	Comment: Elan recommends to also referring to the amendment of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, introduced by Commission Directive 2003/63/EC of 25 June 2003.	Is included by referring to Directive 2001/84/EC "as amended".
124-128	17	Comment: In certain cases, it might be preferable to perform comparative non-clinical studies in the absence of excipients (e.g. to increase the sensitivity of the test system) and thus analysis of the active ingredient of the reference product and the biosimilar might be the better option. Proposed change: Add after line 128**:** **Basically, comparative non-clinical studies should be conducted using medicinal products, however, in certain cases, the use of active ingredient**	Not accepted. This issue is addressed in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues".

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		instead of the medicinal product should be allowed (e.g. in *in vitro* studies) if appropriately justified.	
124-129	11	Comment: In Section 4 "Non-clinical studies" additional information on the requirements (e.g., a minimal number of product lots to be tested in non-clinical studies) is warranted to enhance clarity of the guidance. The draft guidance is silent on the requirement for the reference product source. We would encourage some level of flexibility on the requirement of reference product source (i.e., EU vs. U.S. reference product). Proposed change (if any): Include a minimal required number of lots of the reference product and biosimilar candidate to be used in non-clinical studies.	This is outside the scope of this guideline. Not accepted. A minimal number of product lots to be tested in non-clinical studies cannot be defined a priori. However, an appropriate number of batches, as justified by the applicant, should be analyzed (Also refer to "GL on biosimilars: quality issues" under revision)

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124-195	20	*General comments on Section 4* SUMMARY • At least one animal (at minimum PK/PD/safety) study should generally be mandatory prior to clinical trials of a biosimilar, in order to safeguard human subjects. This mirrors what is done to enable any clinical trial/FIM administration and is in-line with the existing EMA regulatory framework on biosimilars. • Additional factors which may in particular drive the need for animal testing should be included in the guideline (e.g. critical differences in quality attributes or situations where data from analytical and *in vitro* assays or the assays themselves are inadequate; where there is a narrow safety margin with the originator; where a mAb mediates effects *in vivo* that are not yet fully elucidated; when a different expression system is used for manufacturing). • Clear selection and qualification criteria for analytical and *in vitro* assays are lacking in the guideline and should be included. Clarity on the acceptable level of differences would be helpful. It would be appreciated to disclose those requirements in an update of the quality guidance on biosimilars or as part of this draft guidance prior to finalisation.	Overlap with comments from stakeholder 21 in general part. Please see comment on the need for toxicology studies on page 5. Please see comment on additional factors on page 55. Not accepted. Unfortunately, precise levels and criteria for acceptability for each assay that may possibly be used cannot be provided in the Guideline. Data need to be taken together and a judgement on acceptability or sufficient similarity will be based on the totality of data. Refer also to "GL on biosimilars: quality issues, under revision"

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		The draft guidance implies that there are circumstances in which analytical and *in vitro* characterization data would be sufficient to enable entry into human trials. We believe that current analytical and *in vitro* methodologies do not provide sufficient information to properly assess the potential *in vivo* safety and efficacy of mAbs prior to First-in Man trials, and that data from these analyses do not provide an appropriate level of information on structure function relationships. Rather, *in vitro* characterization data are best used to determine the scope of further *in vivo* assessments, or to refer to *in vivo* assessments done previously. In addition, some of the key quality attributes of the biosimilar mAb product such as process and product related impurities and product related substances will differ qualitatively and quantitatively in comparison to the reference product. As has to be done for any biotech product, the biosimilar manufacturer will have to establish acceptance ranges pre-clinically and clinically. As concluded from the draft guidance, comparative human trials are always required in order to demonstrate similar efficacy and safety, even if analytical and *in vitro* similarity have already been shown. However, it is difficult to understand why a comparative animal study (e.g. PK/PD with safety evaluation) should not routinely be requested, as data from this will safeguard patients in clinical trials. As for any product, we suggest that some non-clinical *in vivo* data are necessary prior to entry in human. We do not agree that potential for results that are difficult to	Please see comment on the need for toxicology study on page 5

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		interpret is appropriate justification for not requiring *in vivo* animal studies before entry in human. Comparative non-clinical safety, PK and PD studies can provide critical information to ensure adequate safety prior to clinical testing for biosimilars. The dosing regimen, dose levels, study duration and route of administration should be carefully considered to best identify changes in anticipated safety or pharmacodynamic profiles. PK/PD and safety evaluations should be conducted in a relevant species. In this regards, the following points should be considered: • The Guidance should be explicit about the exceptional circumstances under which all animal studies can be omitted (examples) and should explain how the biosimilar manufacturer can then assure clinical safety for First-In-Human trials. Process, quality, physico-chemical attributes or post-translational modifications will not be identical between the reference and the biosimilar mAb and these factors can impact dose-response relationships in ways that cannot be predicted from *in vitro* data (impact on biodistribution/PK, different (off-target) binding pattern/effects etc.). • The choice of assays will define, and may limit the quality of data generated. Hence, more clarity on the selection and qualification of analytical and *in vitro* assays is necessary. It should be clarified which level of difference is acceptable. If a risk-based approach is to be used for evaluation of	Partly accepted. The GL does indicate when no *in vivo* studies are required and indicate that when needed principles of risk mitigation should be applied when designing the clinical studies. Please see comment on page 130

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		non-clinical safety of the biosimilar mAb, it would be advisable to get more information on risk categorization depending on the mode of action of the mAb (e.g. based on the risk for adverse exaggerated pharmacological *in vivo* effects, the role of effector function driven activities for cell-based targets *in vivo*, expression of target in healthy animal species (if any) vs. disease state, etc.)	
125	21	**Comment:** A risk-based approach is mentioned here, but it is not clear what type of "risk" is supposed to be assessed. In general, this is now regarded too vague, and a detailed explanation on the rationale and practical consequences of this "risk-based approach" is requested. It should be thoroughly justified why animal tox studies are not needed prior to entry in human on biosimilar mAbs, as is requested on other products. **Proposed change (if any):** Type(s) of risk to be taken into account need to be explicitly mentioned and discussed.	Agreed that the terminology 'risk-based' is not entirely clear in the context of a biosimilar approach. The most important issue here is that the level of uncertainty on the clinical safety and efficacy ought to be reduced to an acceptable level. To reach this goal a step-wise strategy is proposed. This step-wise approach simultaneously aims to establish biosimilarity at the non-clinical level. It is understood that this approach could include risk (safety)-related issues, but this needs not necessarily to be so. In the final wording of the guideline the phrase 'risk-based' is no longer used.

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125	17	Comment: The non-clinical development of mAbs as provided in the current draft guideline is viewed as a major step towards reducing the animal testing deemed to be unnecessary based on a very strong scientific background. It is well documented in the scientific literature that there are not many species available which are relevant for *in vivo* studies of mAbs - although there might be a few on a case-by-case basis Furthermore, even if such relevant animal model should exist, in most cases the relevant species would be non-human primates. However, conducting studies in non-human primates would mean difficulty to overcome obstacles for biosimilar developments. More specifically, extensive non-human primate studies to reach statistically powered results can be judged unethical. On the other hand, non-clinical studies with a lower number of non-human primates are hard to interpret, as the statistical comparison of results is not possible. Furthermore, larger animal trials which would provide statistical comparison can be considered as a repetition of already established data for a biosimilar product (shown for the reference product) thus would not bring added value; instead, on the contrary, those would be again unethical. Beyond the limited usefulness of comparative toxicokinetic studies, it is also known that immunogenicity studies built into the *in vivo* non-clinical program would only provide low predictive value regarding immunogenicity in human subjects. Besides	Accepted.

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		the thorough physicochemical characterisation of the process and product related impurities, additional *in vivo* studies addressing the comparability of the impurity profile of biosimilar and reference products would only provide limited value as well. It needs to be emphasized from scientific point of view that a large panel of state of the art *in vitro* assays, in both classes of binding and functional assays, is available to cover all possible bindings of the drug and to cover all the mechanisms of action of the drug. As such, *in vitro* assays are considered as a novel and powerful approach which provide more sensitive tools for demonstrating comparability than animal studies. In addition, the most clinically relevant assays can be selected on a case-by-case basis depending on the indications existing for the particular biosimilar mAb in development.	
125	20	Comment: A risk-based approach is mentioned here, but it is not clear what type of "risk" is supposed to be assessed. In general, this is now regarded too vague, and a detailed explanation on the rationale and practical consequences of this “risk-based approach” is requested. It should be thoroughly justified why animal tox studies are not needed prior to entry in human on biosimilar mAbs, as is requested on other products. Proposed change:	Please see comment from stakeholder 21 above, page 133.

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		Include and discuss type(s) of risk to be taken into account.	
125	22	**Comment:** The Guideline states, "A risk-based approach to evaluate mAb on a case-by-case basis is recommended." This section of the Guideline does not follow other EMA biosimilar guideline principles. Indeed some principles if valid may be relevant beyond biosiomilar monoclonal antibodies and we suggest consideration be given to these remarks in alternative guidelines in Europe.	Agreed. This will be taken into account. Please see ongoing revisions of overarching and general biosimilar Guidelines.
125-129	20	Comment: Additional information on the requirements, e.g., a minimal number of product lots to be tested in non-clinical studies, is warranted to enhance clarity of the guidance. Proposed change: Include a minimal required number of lots of the reference product and biosimilar candidate to be used in non-clinical studies.	Idem as comment to stakeholder 11 on page 129.

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126-127	17	Comment: The concept of performing non-clinical studies is to estimate the risk prior to moving into human trials. However, for biosimilar products, non-clinical studies are more aimed to support the similarity approach and not to determine safety per se. Therefore, it is not understood why there is this strict requirement to perform non-clinical studies before initiating clinical development. Does this mean all studies will have to be final and reports available prior to the start of clinical trials? As rightly mentioned the approach taken will need to be fully justified and therefore the sequence of activities should be under the responsibility of the Applicant depending on the characterisation results of the mAb. Proposed change: ~~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.	Not agreed. For a biosimilar, similarity in Quality and Non-Clinical need to be investigated first. Because biosimilars are quickly given to a large number of patients (i.e. phase 3 trial) at an efficacious dose adequate similarity to the reference product at the quality and non-clinical level has to be ensured. Deletion not agreed. The text is modified: non-clinical studies should be performed before initiating clinical trials.
127 ff	21	**Comment: As outlined above in the "General comments on non-clinical studies",** some of the key quality attributes of the biosimilar mAb product like process related impurities, product related impurities as well as product related substances will differ qualitatively and quantitatively compared to the reference product. Like for any biotech product the	

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		biosimilar manufacturer has to establish acceptable ranges pre-clinically and clinically • More information on the selection, quality and acceptable differences in the results of analytical and *in vitro* tests should be included (see also our remarks in "General NC comments") o Different assay systems may generate different quality of data – how is it assured that state-of-the art standards are met? o Efforts should be taken to make sure the biosimilar mAb has comparable binding profiles, not only to the therapeutic target(s) of the reference mAb, but also to a broad spectrum of other biomolecules. For example, tissue binding tests can help exclude the possibility of unintended binding even though these tests may not be used on a routine basis. It would therefore be helpful, to understand how EMA will ask sponsors to check for unspecific or off-target binding o In addition, binding to molecular targets with high homology to the therapeutic target(s) should be evaluated. o Moreover, if the reference mAb has	Detailed information on quality and acceptable differences in the results cannot be provided, Please see comment to stakeholder20, page 130. Refer to "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (under revision), section 5. related to analytical considerations. Off-target toxicity is a rare event observed in the development of new monoclonal antibodies. Given that the antigen-binding site of biosimilar and reference mAb is identical, different binding profiles (on- and off-target) is not expected. In addition, Fc-dependent binding of biosimilar and reference mAb is compared. TCR is not considered suitable to detect subtle changes in quality attributes. Not agreed, Please see comment above. Agreed. This analysis would then be part of the quality/Non

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		specific claims on target binding specificity among target isotypes that are relevant to clinical efficacy and/or safety, similar binding specificity profile should be required for the biosimilar mAb. ○ Considering the possibility of cross-reactivity and possible different target binding specificity, the toxicology study should be designed not only to investigate toxicities that were reported to the reference mAb, but also to look for additional toxicity signals. **Proposed change (if any):** An *in vivo* non-clinical study should be mandatory; the points above and those in our "**General comments on non-clinical studies"** should be considered.	Clinical comparison in any case. Difference in cross-reactivity and target binding between biosimilar and reference mAb is not expected. Regarding the need for toxicology studies please see previous comment on page 5.
127	20	Comment: Some of the key quality attributes of the biosimilar mAb product like process related impurities, product related impurities as well as product related substances will differ qualitatively and quantitatively compared to the reference product. Like for any biotech product the biosimilar manufacturer has to establish acceptable	Idem, please see above.

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		ranges pre-clinically and clinically. • Different assay systems may generate different quality of data – how is it assured that state-of-the art standards are met? • If the reference mAb has specific claims on target binding specificity among target isotypes that are relevant to clinical efficacy and/or safety, similar binding specificity profile should be required for the biosimilar mAb. • Considering possible different target binding specificity, the toxicology study should be designed not only to investigate toxicities that were reported to the reference mAb, but also to look for additional toxicity signals. Proposed change: Include more specific guidance regarding the decision making process (e.g., decision tree) on the extent of non-clinical studies	

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130	17	Comment: As the approach for the non-clinical studies to be performed will need to be fully justified by the Applicant, there should be flexibility about the sequence of activities to be performed. Proposed change: Delete " = step 1"	Not agreed. *In vitro* should be performed first.
130	22	**Comment:** *In vitro* studies are typically appropriate to evaluate the pharmacology of a medicinal product, but it would be difficult to construe these as studies of pharmacodynamics. **Proposed Change:** We suggest changing the section title to "In vitro **pharmacology** studies = step 1"	Partly accepted. Changed to in vitro studies = step 1.
130-147	11	Comment: In section 4.1 "*In vitro* pharmacodynamic (PD) studies = step 1" we suggest changing the title to "*In vitro* studies = step 1" because some of the listed assays (e.g., FcRn binding) are not directly PD related but rather pharmacokinetic related assessment. We support the emphasis on the comparative nature of all *in vitro* assays. However, the guidance should	Accepted. Agreed.

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		provide some clarity on practical ways to define "difference of importance". We suggest that "difference of importance" should always be based on scientific rationale. Additionally, we suggest lot-to-lot variability of reference products be used to benchmark "difference of importance". In this regard, we ask that the agency provide guidance on the minimal number of innovator batches required to be characterized in order to achieve consistency for different biosimilar sponsors. We appreciate the list of assays (lines 135 -138) required in the *in vitro* comparability studies. We also feel that an additional clarification and guidance is needed for establishing criteria defining acceptable variance in data that are considered fundamental in the assessment of similarity. While we agree with the stepwise approach suggested by guidance to first conduct *in vitro* assays and then *in vivo* studies, as needed, we would appreciate some clarification on how to deal with possible discrepancies between *in vitro* and *in vivo* results. We believe that results from a properly designed *in vivo* study in an appropriate animal model carry more weight and should be considered more important, given that certain *in vitro* assays, although very sensitive, may not have meaningful *in vivo* relevance. Proposed change (if any): We suggest changing the title from "*In vitro*	Please see comment to Stakeholder 11, page 129. Please see comment to Stakeholder 20, page 130. Not agreed. Both *in vitro* and *in vivo* data have to be considered for their own merits. It is also possible that the relevance of a difference observed in a sensitive discriminative *in vitro* assay is greater than the observation of a non-discriminative difference in an *in vivo* study.

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		pharmacodynamic studies" to "*In vitro* non-clinical studies", because some of the listed assays (e.g. ,FcRn binding (Line 136)) are not directly PD related, but rather are important for pharmacokinetic assessment. For each test listed (lines 135-138), please add some criteria for establishing acceptable level of similarity.	Accepted. Please see comment to Stakeholders 20, page130; Precise levels and criteria for acceptability for each assay that may possibly be used cannot be provided in this guideline. Refer to the quality overarching guideline: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (under revision).
130-147	20	Comment: Section "In vitro pharmacodynamic (PD) studies = step 1" refers to some assays, e.g., FcRn binding, that are not directly PD related but rather aid in pharmacokinetic assessment. We suggest revising the title to reflect its broader scope. While we appreciate the list of assays (lines 135 -138) required in the *in vitro* comparative studies, an additional clarification and guidance is needed for establishing criteria defining acceptable variance in data that are considered fundamental in the assessment of similarity. Proposed change: Change line 130 to: "*In vitro* studies = step 1". For each test listed (lines 135-138), please add some	Idem, please see comment above. Accepted. Please see comment to stakeholder 20on page 130.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		criteria for establishing acceptable level of similarity.	
130-194	11	Comment: 4.1 through 4.3: This is presented as three steps whereas there are actually only 2 steps, the *in vitro* pharmacodynamic studies and the *in vivo* non-clinical studies. The strategy step in between to determine whether *in vivo* non-clinical studies are necessary is confusing in this respect.	Not accepted. Only one stakeholder found the 3 steps confusing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
132-147	17	Line 132: Regarding non-clinical development it is suggested that "*number of comparative in vitro studies*" should be carried out. lines 143-144: "*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.*" Comment: There is a rapid increase in the number of potential assays that could be used to address biological activity of mAbs according to state-of-the-art technologies. A reasonable range of assays addressing orthogonal properties that need to be tested on a scientific basis could be pre-defined in biosimilar developments besides the fact that the final set of assays would be determined case-by-case. Since biological assays tend to comprise the most advanced sets of testing methods that have become available, guidance on the acceptable range of applicable test methods including newly developed but not thoroughly established assays would be very helpful.	Partly accepted; Full characterization of binding properties (Fab-dependent and Fc-dependent) should be carried out for any mAb. Selection of functional assays depends on the functional properties of the mAb and will be determined case-by-case. Please see also comment to Stakeholders 20, on page 130. Precise levels and criteria for acceptability for each assay that may possibly be used cannot be provided in the Guideline. Suitability of the assay has to be demonstrated by the applicant. Refer to the quality overarching guideline: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (under revision).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
134	17	Comment: The selection of relevant non-clinical *in vitro* studies should be performed on a case-by-case basis. E.g. for an antibody whose primary mechanism of action is CDC, an in-depth characterisation of downstream signalling events in the target cell should not be necessary. Proposed change: Replace "*In vitro* non-clinical studies should include relevant studies on:" by "*In vitro* non-clinical studies should be conducted according to the individual antibody's functionalities and may include relevant studies on:"	Agreed, Please see comment above. Partly accepted. The introductory wording was not changed. Instead, the list of functional assays to be performed is qualified by "e.g.".
134-138	7	Comment: Various mechanisms in clinical conditions are complex, not fully understood and involve parameters that are not reproduced *in vitro*. The limitation provided by some *in vitro* non-clinical studies should be acknowledged; indeed, some differences detected with *in vitro* studies may not reflect a clinically relevant difference. In addition, the list of *in vitro* studies required may be redundant or overlap with other studies; for example, complement binding is addressed using a cell-based CDC assay that measures the effect of complement activation and subsequent cell killing effect resulting	Limitation is acknowledged in the Introduction, lines, 94-96 and also in lines 188-189 of the draft guideline and is reflected in the final guideline accordingly. Complement binding and CDC assay are not considered redundant, but orthogonal methods to assess the same functional property of the mAb.

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		from the activation of C1q (the first complement protein in the CDC pathway). Conducting a complement binding assay may be redundant and not necessary if the cell-based CDC assay does not detect any significant difference between the reference product and the biosimilar antibody. Proposed change: The final guideline should acknowledge the limitations of some *in vitro* studies (such as FcRn) and the potential for the CDC assay to demonstrate complement binding and activation. It should also be noted that differences between the biosimilar and reference product observed with *in vitro* studies may not automatically reflect clinically relevant differences, but should be thoroughly investigated.	Please see first sentence step 2 (section 4.2).
134-138	15	Comment: Various mechanisms in clinical conditions are complex, not fully understood and involve parameters that are not reproduced in vitro. The limitation provided by some in vitro tests should be acknowledged and indeed some differences detected with in vitro studies may not reflect a clinically relevant difference. In addition the list of in-vitro tests required may be redundant or overlap with other tests – for example, complement binding is addressed using a cell-based CDC assay that measures the effect of complement activation and subsequent cell killing effect resulting from the activation of C1q (the first complement protein in the	Idem, please see comments to stakeholder 7 above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		CDC pathway). Conducting a complement binding assay may be redundant and not necessary if the cell-based CDC assay does not detect any significant difference between the reference product and the biosimilar antibody. Proposed change: The final guidance should acknowledge the limitations of some in vitro assays (such as FcRN) and should acknowledge the potential for the CDC assay to demonstrate complement binding and activation. It should also be noted that differences between the biosimilar and reference product observed with in vitro studies may not automatically reflect clinically relevant differences, but should be thoroughly investigated.	
134-138	21	**Comment:** The parameters to be assessed in Section 4.1 will be assessed using bioanalytical methods, and some of these methods (e.g. ADCC) may have significant intrinsic variability dependent on the design. The risk here is that with a certain setup of these assays (e.g. use of PBMC's as effector cells for ADCC assays) similarity is demonstrated while with another setup (e.g. use of purified NK-cells or FcgammaRIII receptor cell lines as effector cells for ADCC assays) a difference is demonstrated **Proposed change (if any):** It might be useful to define non-clinical similarity of a given mAb biosimilar	Agreed. Please see comment on page 9. Please see comment to stakeholder 20, on page 130130.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to reference product more clearly, and that might work better in mAb product specific guidelines. EMA could consider providing specific guidance around assay qualification/acceptance criteria.	refer also to "GL on biosimilars: quality issues"
134-138	20	Comment: Assays should be carried out using the human target antigens. A list of the human Fc-gamma receptors included in the guidelines would be very helpful. In addition, limitations of specific assays should be addressed. **General limitations of *in vitro* assays:** Some of the listed assays (e.g. ADCC) may have significant intrinsic variability dependent on the design. The risk here is that with a certain setup of these assays (e.g. use of PBMC's as effector cells for ADCC assays) similarity is demonstrated while with another setup (e.g. use of purified NK-cells or FcgammaRIII receptor cell lines as effector cells for ADCC assays) a	Agreed. This is self-evident. Accepted. The list of human Fc-gamma receptors was specified. It is not possible to discuss limitations of individual assays in this Guideline. Agreed. For analysis of ADCC activity of a given mAb, binding to Fcgamma RIIIa and the ADCC assay are considered orthogonal methods. Thus, these assays are considered complementary. However, conclusion on biosimilarity based on conflicting results from the two assays can only be performed on the basis of the actual data. Further recommendations cannot be provided in this

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		difference is demonstrated. **<u>Limitations of FcRn Functional Assessments</u>** FcRn function *in vivo* is complicated. Specifically, FcRn binds the Fc of antibodies, which are then internalized into an acidic compartment from which they are released from FcRn to recycle. The normally used binding assay we are most familiar with is BiaCore- (Surface Plasmon Resonance) based. This assay will provide binding affinity and release kinetics of the tested IgG with the FcRn. Additional simulation to mimic putative cellular mechanism will take on too many presumptive variables and by doing so; will likely add further artificiality to the testing conditions. Though there is a general notion that *in vitro* FcRn binding may correlate to *in vivo* PK behaviour, it is our understanding there is no strong and convincing evidence to indicate this is invariably true. Therefore, while the FcRn binding assay is important as a comparative measure, it does not fully reproduce FcRn function *in vivo* in humans. Therefore, for some antibodies animal PK studies may be useful, and of course human PK studies are ultimately required for this purpose. **<u>CDC Assays Address Complement Binding and</u>**	Guideline. The type of assay used to determine binding affinity to FcRn is not prescribed in the Guideline. For analytical considerations refer to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues, under revision. Not agreed. Literature data indicate a correlation between the affinity of Ig to FcRn and serum half-life (e.g. Dall'Aqua et al. J. Immunol. 2002). Partly agreed. Comparison of PK of biosimilar and reference mAb will be evaluated in an adequately powered clinical study.

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		<u>Activation Functions</u> When considering the possible redundancy of CDC assays and complement binding and activation assays, the molecular details of how antibodies engage and activate the complement system must be considered. Specifically, the CDC assay typically used requires the antibody to bind to C1q (first complement protein on the complement pathway) and induce the complement cascade that leads to cell death. Therefore, the cell-based CDC assay will simultaneously address binding affinity and complement-based killing. As such, it provides a holistic measure of this particular antibody function which is both necessary and should be sufficient for comparative purposes. As far as we are aware, complement binding to antibodies does not have any other function other that activating and enabling CDC. Proposed change: Define non-clinical similarity of a given mAb biosimilar to reference product more clearly. These additional definitions might work better in mAb product specific guidelines. Provide specific guidance around assay qualification and acceptance criteria. Add acknowledgement of the limitations of *in vitro* FcRn binding assays and CDC assays. Given the limitations of the *in vitro* assays, add recommendation that at least	The assays for C1q binding and complement cytotoxicity are orthogonal methods to address the complement-dependent activity of a mAb. Therefore, these assays are considered complementary. Evaluation of C1q binding is required for any mAb as part of the characterization of the Fc binding properties of the molecule. However, a functional assay (either CDC or complement activation) is generally not needed for mAbs directed against non-membrane bound targets. Not accepted. No further definition of the non-clinical similarity is provided in the present Guideline. Not accepted. Please see comment to stakeholders 20, page 130. (Refer to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		one animal study should be carried out for comparative purpose	substance: quality issues, under revision) Not accepted. Please see comments above.
135	21	**Comment:** "Binding to the target antigen" In case the reference mAb binds to multiple targets, it should be required that the biosimilar mAb bind to each target with comparable affinity as the reference mAb. This is important especially if the relative contributions to clinical efficacy and safety have not been established for blocking individual targets. **Proposed change (if any):** Provide clarity around target binding. Clarify requirement to study off-target binding, too.	Partly accepted. Changed to "Binding to target antigen(s)". Off-target toxicity is a rare event observed in the development of new monoclonal antibodies. Given that the antigen-binding site of biosimilar and reference mAb is identical, different binding profiles (on- and off-target) is not expected.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
135	20	Comment: "Binding to the target antigen" It needs to be demonstrated that the biosimilar mAb recognizes and binds to the epitope region of the originator antibody with similar affinity. Some anti-cytokine mAb may also recognize receptor-bound cytokine, therefore, *in vitro* data should include demonstration of the same down stream signalling. In case the reference mAb binds to multiple targets, it should be required that the biosimilar mAb binds to each target with comparable affinity as the reference mAb. This is important especially if the relative contributions to clinical efficacy and safety have not been established for blocking individual targets. Proposed change: Provide clarity around target binding data and requirements to study off-target binding.	Partly accepted. Given that amino acid sequence of biosimilar and reference mAb is identical both molecules have the same antigen-binding region. It is not expected that the biosimilar mAb will bind to a different epitope than the reference mAb. The set of assays for Fab-associated functions depends on the individual product and is therefore described in general terms in the Guideline. Agreed. Text was changed to 'binding to target antigen(s)'. Please see comment to SH 21, page 152.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
135-138	13	130 *4.1. In vitro pharmacodynamic (PD) studies = step1* 131 In order to assess any difference in biological activity between the similar biological medicinal and the 132 reference medicinal product, data from a number of comparative *in vitro* studies, some of which may 133 already be available from quality-related assays, should be provided. Comment: Depending on assay sensitivity and methodology, comparative in vitro studies will always reveal differences in parameters cited in lines 135 to 138 of the draft guide. This is based on the reasonable assumption (based on available publications), that even the Reference Medicinal Product itself will vary between every batch, in for example the ratio glycosylated proteins and the level of glycosylation, refer also to [(1)]. Therefore the cited parameters will vary (slightly) for each batch of the Reference Medicinal Product or the Biosimilar, (again assuming sufficiently high assay sensitivity and methodology). Proposed change (if any): A statement at the beginning of section 4.0 should	Proposed changes not accepted.

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		incorporate the following: 1.) "the Biosimilar requires to such an extend similarity to the Reference Medicinal Product, as the Reference Medicinal Product is similar to itself, when compared on a batch to batch basis, as the optimum. Deviation of this approach is generally acceptable, but requires justification and possibly additional clinical evaluation in order to assess associated risks" Further to guide the industry and to avoid unnecessary costs and disappointments, it should be stated that: 2.) "For non clinical setting it is advisable that the "Quality Profile", (refer to [(1)]) of the Biosimilar is within the levels of variation observed for the "Quality Profile" of the Reference Medicinal Product. Thoroughly determination of the "Quality Profile" of the Reference Medicinal Product can be used to set the margins of tolerance (for variation) for the Biosimilar "Quality Profile". Deviation of this approach is generally acceptable, but requires justification and possibly additional clinical evaluation in order to assess associated risks". By adopting this proposed approach, the level of comparability between the Reference Medicinal Product and the Biosimilar, using sound, measurable and justified parameters will reduce risks associated with clinical trials and will likely lead to (at least) a similar efficacy and safety profile of the Biosimilar in clinical	These topics are addressed in the " Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues " which is currently under revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		trials compared to the Reference Medicinal Product	
136	1	Comment: The request for binding studies to *all* Fcgamma receptors seems not necessary and in addition hard to meet with respect to the extensive number of receptors that are known. It might be justified to restrict this requirement to the well characterized FcγRI (CD64), FcγRIIA (CD32), FcγRIIB (CD32), FcγRIIIA (CD16a), and FcγRIIIB (CD16b) receptors as they cover the complete binding region for all Fcγ receptors on the biosimilar mAb. Proposed change (if any): Please rephrase the sentence as follows: "Binding to representative isoforms of the relevant three Fcgamma receptors, FcRn and complement."	Change accepted. In addition, Fcg receptors are specified in the Guideline (FcγRI, FcγRII, FcγRIII).

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136	17	Comment: The request for binding studies to *all* Fcgamma receptors seems not necessary and in addition hard to meet with respect to the extensive number of receptors that are known. Furthermore, not all might have a relevant functionality. Therefore, it might be justified to restrict this requirement to the well characterised FcγRI, FcγRII, FcγRIII receptors as they cover the complete binding region for all Fcγ receptors on the mAb. If biosimilarity can be shown regarding the cited receptors above, also additional Fcγ receptors will most likely show comparable binding properties. Therefore they serve as surrogates for the other Fcγ receptors. Proposed change: Please rephrase the sentence as follows: "Binding to ~~all~~ **representative isoforms of the appropriate three** Fcgamma receptors, FcRn and complement."	Change accepted. In addition, Fcg receptors are specified in the Guideline (FcγRI, FcγRII, FcγRIII).
137-138	20	Comment: "Fab-associated functions (e.g. neutralization, receptor activation or receptor blockade); Fc-associated functions (ADCC and CDC assays, complement activation)" It is important to note that different assays can generate different results with regards to *in vitro* similarity for the reference and biosimilar mAbs. The	Guidance on analytical considerations is provided in the " Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality

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		necessity to carry out of head-to-head studies, as well as selection, optimization, justification, and validation of the *in vitro* testing system should be discussed/ reference to appropriate guidance given. It is not always clear how data from such Fab and Fc functional assays translates into clinical safety and efficacy. Thus, an *in vivo* safety assessment study should also be required Proposed change:. Consider in vivo testing as default requirement and provide more specific recommendations on assay selection and quality. Fab-associated functions may also include induction of apoptosis. Fc-associated functions may also include cytokine release and increase of apoptosis. It should be acknowledged that Fc associated function relevant to the MoA of the originator antibody should to be tested.	issues", under revision. Change not accepted. Given the multitude of mAbs, detailed guidance cannot be provided on which type of functional assay has to be performed for a given mAb. The guidance states that the in vitro studies should broadly cover all functional aspects of the mAb. Default *in vivo* testing is not accepted (Please see comments on page 5).
137-138	21	**Comment:** "Fab-associated functions (e.g. neutralization, receptor activation or receptor blockade); Fc-associated functions (ADCC and CDC assays, complement activation)" It is important to note that different assays can generate different results with regards to *in vitro*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		similarity for the reference and biosimilar mAbs. The necessity to carry out of head to head studies, as well as selection, optimization, justification, and validation of the *in vitro* testing system should be discussed/ reference to appropriate guidance given. It is not always clear how data from such Fab and Fc functional assays translates into clinical safety and efficacy. Thus, an *in vivo* safety assessment study should also be required **Proposed change (if any):**. More clarity on selection and assay quality should be provided in the guidance.	Not accepted. Guidance on analytical considerations is provided in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues, under revision.
139-142	5	Comment: We agree in general with the discussion in § 4.1 of the purpose and scope of comparative *in vitro* testing of biosimilars and reference products. We recommend that the CHMP include a discussion of margins for this testing. These margins should be prespecified and tight, and they should be driven by the sensitivity and precision of the assay being used. We also agree in particular with the observation on lines 145-147 that this testing, although fundamental and necessary, may not fully elucidate a product's *in vivo* characteristics. We recommend that the guideline	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clarify that non-clinical concentration/activity studies cannot by themselves fully exclude all differences of importance in the concentration-activity relationship between the products. Proposed change (if any): "These concentration/activity studies should be comparative in nature and should be designed ~~to exclude~~ **to detect and measure** ~~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. **Equivalence margins must be defined *a priori* and appropriately justified. The narrowness of the margins should be dictated by the sensitivity and precision of the assay being used.** **Moreover, it should be understood that non-clinical concentration/activity studies may not fully exclude all differences of importance in the concentration-activity relationship between the products and that these differences may become apparent only upon human testing."**	Partly accepted. The sentence was rephrased to "studies … should be designed to be sensitive enough to detect differences in the concentration-activity-relationship." For definition of equivalence margins refer to the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues", under revision. Not included. The sentence does not provide further recommendation on the *in vitro* testing.
139-142	20	Comment: **Please reword:** "These ~~concentration/activity~~ studies	Partly accepted.

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		should be comparative in nature and should be designed to ~~exclude~~ identify 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." It is not fully understood what this paragraph means. The methods & data interpretation processes that it refers to are not standardized, and it is often not clear how (if?) such functional assay data can be used to accurately predict clinical safety and efficacy. It is often unreasonable to expect to know how data from these *in vitro* methods translate differences into clinical differences. Proposed change: Suggest including acceptable limits for comparison with the innovator product.	The sentence was rephrased to "studies … should be designed to be sensitive enough to detect differences in the concentration-activity-relationship…" Not accepted. For definition of equivalence margins refer to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues", under revision.
139-142	22	**Comment:** The Guideline states, "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."	Not accepted.

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		Acceptable levels of comparability could be clarified, including a suggestion that a high degree of similarity is expected.	For definition of equivalence margins refer to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues", under revision".
139-142	21	**Comment:** "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." It is not fully understood what this paragraph means. The methods & data interpretation processes that it refers to are not standardized, and it is often not clear how (if?) such functional assay data can be used to accurately predict clinical safety and efficacy. It is unreasonable to expect to know how data from these *in vitro* methods translate differences into clinical differences. *In vitro* work should gate animal studies, then animal studies should gate clinical studies. Good *in vitro* data does NOT alone justify bypassing *in vivo* work. The biosimilar manufacturer has to show that their data are scientifically adequate. In addition, the biosimilar sponsor must demonstrate that their methods and methodologies are state-of-the-	BMWP agrees that the Applicant has to show their data are adequate and sufficient. Bypassing *in vivo* studies is not an aim of *in vitro* studies. All data should establish similarity and support clinical studies. If the *in vitro* data are sufficient, there is no need for *in vivo* data.

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		art/consistent with industry best practices. **Proposed change (if any):**	
143-144	1	Comment: The same as above holds true for the request to investigate *all* functional aspects. The requirement that all functional aspects have to be covered even though some may not be considered necessary for the mode of action seems too much. Especially since also extensive physicochemical characterization is performed. Moreover, the results will be difficult to interpret if differences occur, especially if the mode of action is not considered to be clinically relevant. Clarification on effector in vitro assays is needed: some times it makes no sense to do ADCC or CDC when the target is not expressed on membrane. In addition, an added value of these artificial systems is not seen. Proposed change (if any): Please rephrase the sentence as follows: "Together these assays should cover broad functional aspects to extensively characterize the mAbs even though some aspects may not be considered necessary for the mode of action in the clinic. However, artificial systems, e.g. ADCC or CDC when the target is not	Partly accepted. Sentence was rephrased as follows: "Together these assays should broadly cover the functional aspects of the mAb, even though…". Statement was included that "evaluation of ADCC and CDC is generally not needed for mAbs directed against non-membrane targets".

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		expressed on the membrane, should not be pursued.”	
143-144	17	Comment: The request for binding studies to *all* Fcgamma receptors seems hard to meet with respect to the extensive number of receptors that are known. The same as above holds true for the request to investigate *all* functional aspects. Moreover, the results will be difficult to interpret if differences occur, especially if the mode of action is not considered to be clinically relevant. We need to have clarification on effector *in vitro* assays: some times it makes no sense to do ADCC or CDC when the target is not expressed on membrane. Proposed change: Please rephrase the sentence as follows: “Together these assays should cover ~~all~~ **as many** functional aspects **as reasonably possible to extensively characterise** ~~of~~ the mAbs even though some **aspects** may not be considered necessary for the mode of action in the clinic. **Non physiological assay systems should not be pursued.”**	Partly accepted. Sentence was rephrased as follows: "Together these assays should broadly cover the functional aspects of the mAb, even though…". A statement was included that "evaluation of ADCC and CDC is generally not needed for mAbs directed against non-membrane bound targets".
143-146	20	Comment: Are the all functional aspects of all mAbs known? The draft guidance is a bit contradictory here.	Agreed, that not all functional aspects of a mAb are known. Sentence was rephrased (Please see comment above)

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		Proposed change: Consider revision. Product specific guidelines might be useful to clarify on which mAbs the effects are unknown.	
143,146	21	**Comment:** Are the all functional aspects of all mAbs known? Consider revision. Product specific guidelines might be useful also to clarify on which mAbs the effects are unknown. **Proposed change (if any):**	Agreed, that not all functional aspects of a mAb are known. Sentence was rephrased (Please see comment above)
146	11	Proposed change (if any): For clarity, "non-clinical" should be added after *in vivo* to make clear that it applies to *in vivo* non-clinical studies.	Not accepted. This could also be clinical.
146-147	4	Comment: How can mechanisms which are not fully elucidated play a role in a similarity exercise? Proposed change (if any): delete sentence	Partly accepted. Rephrased sentence.
148-149	17	Comment: Same comment as for line 130 Proposed change:	Not accepted. This is clear to most stakeholders.

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		Delete " = step 2"	
148-163	11	Comment: Section 4.2 "Identification of factors of importance for the *in vivo* non-clinical strategy = step 2" indicates that *in vivo* (PK/PD, toxicology) studies may not be needed unless factors of important differences have been identified. This approach is not supported by our experience to date and our position is that at least one *in vivo* animal PK (and PD if feasible) study is needed prior to clinical studies. If the *in vivo* PK/PD data, along with *in vitro* data, demonstrate biosimilarity, then conducting toxicology studies should not be required. Please consider revising recommendations and wording in section 4.2 of the draft guidance. In addition, more guidance is needed on how to address possible discrepancies between *in vitro* and *in vivo* results. We believe that results from a properly designed *in vivo* study in an appropriate animal model carry more weight and should be considered more important, given that certain *in vitro* assays, although very sensitive, may not have meaningful *in vivo* relevance. Proposed change (if any): At minimum one *in vivo* (non-terminal) animal PK (and PD if feasible) comparative study should be performed to support first-in-human studies. We also suggest adding "*in vitro* non-clinical assay difference" as another factor to be considered for conducting *in vivo* studies, considering that some *in vitro* differences are	It is not agreed that always an *in vivo* study should be performed. If biosimilarity can be sufficiently demonstrated based on physicochemical tests and *in vitro* assays, an *in vivo* study would not add relevant information.

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		to be expected given the complex nature of mAb structure.	
148-163	15	Comment: This section is very scientific, and consistent with biosimilar development principles, which hold that in vitro studies are a more sensitive way of detecting differences between a biosimilar antibody and the reference product. However, the perspective of this section is focused on the final data package required to support approval. We recognize this is consistent with the EMA's focussed authority, which does not extend to the oversight of clinical trial conduct in EU Member States. We further recognize that if sensitive in vitro comparator assays are available, and if PK similarity and clinical similarity are shown in humans, in vivo animal data are likely to not play a major role in approval decisions, which are within the EMA's purview. However, in order to conduct the required human trials, some national authorities may feel that non-clinical data packages will be required in all instances to support the conduct of human PK and comparative clinical trials. Further, in some EU Member States, and in many non-EU countries that may refer to this first guidance on biosimilar antibodies, it could remain an expectation that these data packages contain at least some comparative PK and toxicology data from animal studies even if scientific considerations support not	Indeed decisions on approval for clinical trials are within the remit of the national authorities. It is however the view of the BMWP that *in vivo* animal studies should not be performed if these do not add relevant information. BMWP therefore believes that the proposed step-wise approach is also applicable throughout clinical development of biosimilar MAbs.

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		conducting such studies. Given this, some comment in the final guidance regarding the non-clinical study requirements (if any) to initiate clinical development would be a valuable addition to the final guidance. Again, we recognize that oversight of clinical trial conduct is outside of the EMA's purview. However, some general concepts regarding the non-clinical study(s) that are considered scientifically valid to support various clinical trial scenarios would be very useful to product developers and would facilitate the development of these products. Proposed change: To facilitate clinical development in EU Member States a new section should be added to address (in general terms) the in vivo non-clinical safety and PK data that would be considered as appropriate (if scientifically justified) to support various clinical scenarios. These clinical scenarios could include initiation of clinical development in healthy volunteers versus patients and at the full labelled dose rather than the standard dose escalation studies typically required for new entities.	The Guideline is also applicable for other phases of clinical development.
148	21	**Comment:** "Identification of factors of importance"… There are more potential "factors of importance" that should be added into this list. **Proposed change (if any):**	It is indicated in the guideline that results form *in vitro* assays should be satisfactory. That studies should be state-of-the-art, is a general expectation relevant for all applications. Presence of relevant quality attributes that have not been detected in the reference product (e.g new post-translational

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		These additional factors which may drive the need for animal testing should be included in the guideline: • situations where data from *in vitro* assays or the assays themselves are inadequate (selection and quality of tests need to be defined and state-of-the art); • when there is an expression system different to the originator; • where there is a narrow safety margin with originator; → Clear selection and qualification criteria for analytical and *in vitro* assays are lacking in the guideline and should be included. → Analytical and *in vitro* methods determining similarity must be rigorously developed to current state-of-the-art standards and qualify for "fitness for purpose"; to us, more clarity is needed on which level of difference between originator vs biosimilar is acceptable;	modification structure)is mentioned as a factor to be considered. A narrow safety margin might be a factor to be considered when slight differences are seen *in vitro*. It is currently not possible to provide discrete cut-off values for acceptability of 'levels of differences'. Products should be similar, which will be judged based on the whole data package. Please refer to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues"
148 ff	21	**Comment:** Differences in *in vivo* behaviour of mAbs may be triggered also by differences in post-translational modifications such as glycosylation and/or e.g. changes leading to differences in charge. These factors may not be picked up in the *in vitro* studies described in 4.1. Therefore, differences in post-	Different glycosylation patterns and differences in charges may result from differences in post-translational modifications. If these affect biological activity of either Fc or Fab functional parts, these should be picked up in relevant *in vitro* assays.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		translational modifications and/or charge should be added to the list of factors under 4.2. **Proposed change (if any):** Add to the factors to be considered: "Differences in post-translational modifications such as glycosylation and/or differences in charge"	
148 ff	21	**Comment:** There is no mention of evaluating nonclinical *in vivo* PK in Step 1 & 2 to trigger additional step 3 *in vivo* nonclinical evaluation. Simple *in vitro* PD studies and factors identified in Step 2 should not be the only triggers for *in vivo* evaluation. **Proposed change (if any):** The association of *in vitro* functional parameters and consequences on *in vivo* PK/PD and toxicity will need to be part of the assessment in determining the need for additional *in vivo* nonclinical studies. In cases where *in vitro* characterization is similar or subtle changes are observed, follow up comparative nonclinical toxicology study(ies) should be performed to understand all safety risks and identify additional nonclinical toxicity studies that need to be conducted prior to exposing humans. This would be followed by clinical assessment in order to understand how these in-vitro changes translate	When *in vitro* data are similar, usually, there is no need to follow-up with *in vivo* studies. If there are slight differences, the level of uncertainty on the *in vivo* impact should determine the need for *in vivo* studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinically.	
148-163	20	Comment: "Identification of factors of importance"… There are more potential "factors of importance" that should be added into this list. This section indicates that *in vivo* (PK/PD, toxicology) studies may not be needed unless factors of important differences have been identified. This approach is not supported by our experience to date and our position is that at least one *in vivo* animal study (e.g., PK/PD with safety evaluation if feasible) is needed prior to clinical studies. If the *in vivo* PK/PD/safety data, along with *in vitro* data, demonstrate biosimilarity, then additional animal studies should not be required, in-line with the existing EMA biosimilar regulatory framework. Please consider revising recommendations and wording in section 4.2 of the draft guidance. In addition, more guidance is needed on how to address possible discrepancies between *in vitro* and *in vivo* results. We believe that results from a properly designed *in vivo* study in an appropriate animal model carry more weight and should be considered more important, given that certain *in vitro* assays, although very sensitive, may not have meaningful *in vivo*	Please see comments on pages **Error! Bookmark not defined.** and **Error! Bookmark not defined.**.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relevance. Proposed change: Additional factors which may drive the need for animal testing include: • Critical differences in quality attributes (e.g., in post-translational modifications such as glycosylation and/or changes leading to differences in charge); • Where data from analytical and *in vitro* assays or the assays themselves are inadequate (selection and quality of tests need to be defined); • Where a mAb mediates effects *in vivo* that are not yet fully elucidated; • Where there is a narrow safety margin with originator; Because of uncertain relevance of some *in vitro* data to the *in vivo* activities, at minimum one *in vivo* (non-terminal) animal PK (and PD with safety evaluation if feasible) comparative study should be performed to support FIH studies.	Please see comments on page 168
150 - 161	4	Comment: Should the models not be validated for their ability to discriminate between the differences discussed here?	Studies should be state-of-the-art and scientifically sound and data should be reliable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
150-161	22	**Comment:** We suggest that this section be extended to clarify that *in vivo* mechanisms of action are not fully elucidated for some mAbs. This has been recognized in lines 146-147 ("It is acknowledged, however, that some mAbs may mediate effects in vivo in ways that are not yet fully elucidated.") and merits inclusion in the list of critical factors to evaluate. One risk factor that is notable for its absence is the potential for the mAb to induce a severe immunological response (*i.e.* acute reactions, separate from the formation of ADAs). If such was observed for the reference product, it would seem prudent to evaluate the comparative toxicity of the biosimilar *in vivo* regardless of the presence or absence of the other risk factors. **Proposed Change:** We suggested the additional bullets: • **<u>"Reference to an acute toxicity or off-target reactions.</u>** **<u>If known toxicity exists for the reference product, then a comparative toxicity study should be conducted."</u>**	For clarity, the line to which the respondent refers has been moved to this section. Issues of hypersensitivity are difficult to assess, also in animal studies. BMWP does not support comparative toxicity studies for biosimilars.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
150-163	7	Comment: It is suggested that this section is extended to clarify that *in vivo* mechanisms of action are not fully elucidated for some mAbs. One important factor that is notable for its absence is the potential for the mAb to induce a severe immunological response (i.e. acute reactions, separate from the formation of ADAs). If such was observed for the reference product, it would seem prudent to evaluate the comparative toxicity of the biosimilar *in vivo* regardless of the other risk factors being considered.	Not agreed. Issues of hypersensitivity are difficult to assess, also in animal studies.
152-151	2	Comment: It is difficult to imagine, that a different cell expression system such as yeast, plant, insect, etc. may still be covered under similar biological medicinal products Proposed change (if any): Delete 152-153	This paragraph has been reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
152-153	4	Comment: Here the potential relevance of different expression systems on the quality of the product is mentioned. However as it is stated now, it appears that the presence of different impurities is most relevant in this respect. Although these impurities may potentially be of importance with respect to immunogenicity, this aspect can currently not be adequately evaluated in non-clinical studies. In our view differences between the reference mAb and the biosimilar mAb themselves could potentially be of importance, e.g. a different glycosylation pattern. Furthermore the differences in process- and product-related impurities is already highlighted in the next bullet point. We propose to adapt these line as follows: Proposed change (if any): • ~~Differences in process related impurities due to~~The use of a different cell expression system compared with the reference medicinal product (e.g. yeast, insect, plant, vs. mammalian expression system)~~.~~ leading to different post-translational modifications e.g. glycosylation patterns.	Partly accepted. This paragraph has been reworded taking into consideration this comment and other comments raised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
152-153, 415-419	5	Comment: The draft guideline would permit applicants to use a different cell expression system for biosimilars from that used to manufacture the reference medicinal product. (Separately, it seems to permit the use of a cell expression system as to which there is "limited experience" in humans.) Use of a different host cell system raises the strong possibility of different post-translational modifications, as well as qualitative and quantitative differences in impurity profiles. As a result, there is a significant possibility of a different immunogenicity profile and the potential for other clinically important differences as well. In view of the principles that a proposed biosimilar should be as similar to the reference product as is reasonably achievable and that avoidable differences should be prohibited, the CHMP should not permit biosimilar applicants to use different cell expression systems. Use of the same species and tissue type should be required. Proposed change (if any): Lines 152-153 and the two sentences on lines 415-419 ("Study of unwanted immunogenicity . . . regulatory authorities.") should be deleted. In a new discussion of the quality characteristics of biosimilar mAbs, insert the following: **"Use of the same species and tissue type for the cell expression system is expected."**	Not accepted. Please refer to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
152-153	15	Comment: With regards to the listed factors to be considered for the need for additional in vivo non-clinical studies (e.g., "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)"), in some instances differences of some process-related impurities may not manifest through in vivo non-clinical tests. Proposed change: Please clarify in the final guideline.	Agreed. Indeed, a potential outcome that could be anticipated due to differences in process-related impurities is a difference in immunogenic potential or the potential to cause hypersensitivity. Both effects are difficult to predict from animal models.
152-155	20	Comment: "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)." This is oversimplification. Differences in process-related impurities exist always (and usually also in product related impurities), since the production cell and manufacturing processes are different. This in itself justifies performing comparative non-clinical studies *in vivo*. Process related impurities are process dependent and need to be considered in the context of their relevance, primarily in terms of impact on safety. It should be the biosimilar manufacturer's responsibility to thoroughly identify impurities and to provide data to	Partly accepted. The section related to factors of importance has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		show that differences in impurity profiles do not pose risks to efficacy and safety. Factors to trigger *in vivo* studies include differences in process-related impurities due to different cell expression system. The limitation to process-related impurities to those derived from different cell expression systems is not understood. *Any* differences in the impurity profile should trigger *in vivo* studies, irrespective on the root cause Proposed change: Remove ”to a different cell expression system compared with the reference medicinal product (e.g. yeast, insect, plant, vs. mammalian expression system)” Consider adding product related impurities?	
152-155	21	**Comment:** “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).” This is oversimplification. Differences in process-related impurities exist always (and usually also in product related impurities), since the production cell and manufacturing processes are different. This in itself justifies performing comparative non-clinical studies *in vivo*. Process related impurities are process dependent and need to be considered in the context of their relevance, primarily in terms of impact on safety. It	Please refer to the comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be the biosimilar manufacturer's responsibility to thoroughly identify impurities and to provide data to show that differences in impurity profiles do not pose risks to efficacy and safety. Factors to trigger *in vivo* studies include differences in process-related impurities due to different cell expression system. The limitation to process-related impurities to those derived from different cell expression systems is not understood. *Any* differences in the impurity profile should trigger *in vivo* studies, irrespective on the root cause **Proposed change (if any):** Remove ”to a different cell expression system compared with the reference medicinal product (e.g. yeast, insect, plant, vs. mammalian expression system)” Consider adding product related impurities?	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
154	11	Proposed change (if any): With respect to "product- and/or process related impurities", we suggest adding "e.g., glycosylation and charge differences," after that phrase. The rationale for this is as follows: 1) these two types of product modifications are common and highly dependent on the expression system and purification process, 2) they may impact pharmacokinetic and pharmacodynamic properties of a molecule, and 3) their potential impact on PK and PD may not be detected by the *in vitro* non-clinical assays described in Section 4.1.	This item has been removed from the Guideline.
154-155	15	Comment: With regards to the listed factors to be considered for the need for additional in vivo non-clinical studies, please provide further clarification with regards to the factor, “presence of a mixture of product- and/or process related impurities that can be less well characterized”. Would identification thereof automatically point toward the need for in vivo studies?	Not accepted. This item has been removed from the Guideline. No please refer to lines 162-163 of the draft Guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
156	5	Comment: The draft guideline would permit a similar biological medicinal product to have "[s]ignificant differences in formulation" from the reference medicinal product. Significant differences in formulation (for example, excipients) can lead to differences in stability, pharmacology, bioavailability, and immunogenicity. In view of the principles that a proposed biosimilar should be as similar to the reference product as is reasonably achievable and that avoidable differences should be prohibited, the CHMP should not permit biosimilar applicants to use different formulations. Proposed change (if any): "~~Significant differences in formulation, use of not widely used excipients.~~ **Differences in formulation, which in any case should be minor and unavoidable."**	Not accepted. Differences in formulation can be accepted if the applicant succeeds in showing comparability to the reference product.
156	11	Comment: Please consider adding a description or explanation of the term "use of not widely used excipients". Proposed change (if any): Please provide more specific criteria for excipients that would be viewed as "not widely used".	Partly accepted. Adapted to " not widely used for mAbs"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
156	17	Comment: "Not widely used" is not defined – the proposed wording is better compatible with the guideline on excipients (EMEA/CHMP/QWP/396951/2006) **Proposed change**: Change wording to: "Significant differences in formulation, use of ~~not widely used~~ **novel** excipients."	Not agreed. Excipients not widely used in mAbs are meant here.
156	20	Comment: Please consider adding a description or explanation of the term "use of not widely used excipients". In addition, some examples of differences in formulation that could be considered significantly different would be very helpful. Proposed change: Provide more specific criteria for excipients that would be viewed as "not widely used". Provide examples of what would be considered a significantly different formulation and what would not.	Please refer to the above comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
157-158	5	Comment: The draft guideline identifies several factors to be considered when determining the extent of necessary *in vivo* studies, including "the need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers." This sentence is unclear as to whether the factor to be considered is the type of subject (patient or healthy), the dose, or the relationship between these two factors. Proposed change (if any): We recommend that this sentence be clarified.	Accepted. This bullet point has been removed.
157-158	10	Comment: These lines refer to the need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers. This aspect identified as a factor of importance for the *in vivo* non-clinical strategy is understood as a factor that would trigger the need for specific *in vivo* considerations and studies because of the ethical aspect of testing therapeutic doses in patients rather than healthy volunteers. Because of the nature of mAbs, Elan recommends to also refer to the guidance document of July 2007 on strategies to identify and mitigate risks for first in human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07). From a specific standpoint, the probability to demonstrate the non-clinical similarity with a reference	Partly accepted. This item has been removed. However, the principles to mitigate any potential risk in clinical studies are mentioned in the final guideline.

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		product is limited due to the complexity of the molecules and processes, limitations in methodology (analytical, biochemical, potency, PK/PD).	
157-158	11	Comment: With respect to the factor of testing biosimilars directly in patients vs. healthy volunteers, please provide some clarification and rationales on how the need to test the biosimilar mAb directly at therapeutic doses in patients vs. healthy volunteers dictates the need for, and the type of certain *in vivo* nonclinical studies. Should this be interpreted that the healthy volunteer scenario indicates a lower clinical risk, justifying less extensive *in vivo* nonclinical comparative studies?	Please see previous comment.
157-158	17	Comment: It is not clear why testing of the biosimilar mAb at therapeutic doses in patients should trigger *in-vivo* non-	Please see previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical testing in contrast to testing in healthy subjects where in the later population also therapeutic doses are being investigated. The decision to perform additional *in-vivo* non-clinical studies should be based on results of the quality testing as well as *in-vitro* non-clinical data. Proposed change: ~~**Th**e need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers~~	
157-158	20	Comment: **"**The need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers". This point is not clear – please explain why these scenarios would be different regarding the need for animal studies before exposure to human. Is it the potential risk-benefit for patients compared to healthy volunteers that is the driver for the decision or is it the potential difference in dose (i.e., therapeutic dose vs. dose escalating in healthy subjects) ? Proposed change: Revise the text, e.g.: "The need to test the biosimilar mAb directly at a therapeutic dose in patients, *or a desire to start human trials directly at the approved dose, or the need to initiate human trials with multiple*	Please see previous comment.

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		dose study designs, should all be considered as potentially increasing the importance of having supportive in vivo non-clinical safety data prior to trial initiation."	
157-158	21	**Comment:** "The need to test the biosimilar mAb directly at a therapeutic dose in patients, rather than in healthy volunteers". This point is not clear – please explain why these scenarios would be different regarding the need for animal studies before exposure to human. **Proposed change (if any):** Please clarify/ remove this point	Please see previous comment.
159-161	1	Comment: It is important to have relevant in vivo models if additional in-vivo nonclinical studies are considered. However, solely the availability of these models should not be an argument to justify the need for additional studies. Therefore this general statement should not be a bullet point but rather be added after the last sentence in this paragraph (line 163) as a general comment. Proposed change (if any): Delete last bullet point (lines 159-161): "Availability of	Partly accepted. Removed as bullet point.

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		a relevant in vivo model……and reference mAb". Insert in line 163 after "…and need for in vivo testing." "The in vivo model should be relevant (with regards to species or design, e.g. transplantation models) and likely capable of providing interpretable data on similar in vivo behaviour of biosimilar and reference mAb."	
159-161	11	Comment: With respect to availability of relevant species, we recommend adding a statement acknowledging that some animal models that may not be appropriate for PD studies could be relevant for comparison of pharmacokinetic properties of biosimilar and reference products. Even in the absence of a relevant animal model for PD, there is still a need for *in vivo* PK study in some species. These types of animal model may be of particular importance for understanding the potential impact of differences on the less understood attributes related to mAb disposition	Not accepted. Studying PK in a non-relevant species would only be of very limited value. Removed as bullet point Focus of the study (could be PK only) is explained in step 3.
159-161	17	Comment: The existence of an animal-model should not be a factor for requesting in-vivo studies per se. Proposed change: ~~"Availability of~~ **If biosimilarity may not sufficiently be established using in-vitro testing,** a relevant in-vivo model (with regard to species or design, e.g.	Partly accepted. Bullet removed.

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		transplantation models) which is likely capable of providing interpretable data on similar *in vivo* behaviour of biosimilar and reference mAb **may be considered."**	
164	17	Comment: Same comment as for line 130 Proposed change: Delete " = step 3"	Not accepted. Only 1 stakeholder found the 3 steps confusing.
164-168	11	Comment: Section 4.3 "*In vivo* studies = step 3" indicates that *in vivo* animal study should be performed only based on the outcome of steps 1 and 2. As stated above, we believe that one *in vivo* animal PK (and PD if feasible) should be performed as a default. Please consider revising recommendations and wording in section 4.3 of the draft guidance. Proposed change (if any): At minimum one *in vivo* (non-terminal) animal PK (and PD if feasible) comparative study should be performed to support first-in-human studies.	Not accepted. It is not clear why an *in vivo* animal PK (and PD) should be performed as a default. Rather, only if a certain question needs to be investigated, an in vivo study needs to be performed. If an in vivo study is needed, the focus of the study could be PK and/or PD and/or safety. Safety does not refer to a classical toxicology study here, but is intended as clinical safety observations.
164-194	5	Comment: The guideline discussion of *in vivo* studies begins with the observation that if the comparability exercise in *in vitro* studies is "satisfactory" and no "factors of concern" are identified, *in vivo* studies will not be	Not accepted. Revision of the overarching guideline is ongoing. If clear differences would be observed in PK/PD, the conclusion would be that this is not a biosimilar.

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		needed. This is inconsistent with the CHMP's non-clinical and clinical guideline, which does not permit biosimilar applicants to omit *in vivo* studies. We believe it also conflicts with the reasonable expectations of individuals enrolled as study subjects (i.e., that animal safety testing will have been conducted). The CHMP should not permit testing of any biological product in humans without at least some toxicology testing in another species. The nature (i.e., comparative or noncomparative) and extent (i.e., multiple dose levels or single dose level) of the studies should be determined on a case-by-case basis. If the CHMP does permit the first *in vivo* testing of a new product to be in humans, it should require that the study subjects be informed that there has been no prior animal testing. Proposed change (if any): Lines 165-168 should be deleted, and the CHMP should make it clear that some *in vivo* testing will be required before any biosimilar product may be first administered to humans. The rest of § 4.3 should be revised accordingly. For example, we recommend the CHMP add the following sentence in the middle of line 181: **"If the mAb exhibits nonlinear PK or an abnormal dose-response relationship, *in vivo* toxicology studies should involve multiple dose levels."**	
164-196	15	Comment Because it is expected that the understanding of immunogenicity requirements will continue to evolve,	Not accepted. This is not within the scope of this guideline. Please see 'Guideline on Immunogenicity assessment of

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		we are in agreement with the current level of detail in the guideline. However, if additional granularity is added to the document following receipt of all comments, we would recommend the following: For the immunogenicity bioanalytical assay, two assays should be developed: one designed to test for antibodies against the originator reference product and one designed to test for antibodies against the biosimilar. The same positive control may be used to monitor performance of both assays. Samples from study subjects should be tested in the assay that is specific for the product with which the study subject was dosed. If a subject is positive for antibodies against the product dosed, cross-reactivity against the alternative product should be assessed in the alternative assay.	monoclonal antibodies intended for in vivo clinical use'.
165-168	17	Comment: Same comment as for line 130, 148-149, 164 Proposed change: 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~~ **the data evaluated according to sections**	Not accepted. Mentioning the steps is not confusing to most stakeholders.

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		4.1 and 4.2 raises concerns, the need for comparative *in vivo* studies should be decided case-by-case.	
165-168	22	**Comment:** We suggest that the Guideline clarify and add that *in vivo*, non-clinical evaluation should be a default expectation unless the sponsor can justify the absence. We suggest the Guideline clarify that the intention to omit *in vivo* studies prior to human exposure requires scientific advice to confirm the acceptability of such an approach. **Proposed Change:** We suggest the alternative text in lines 165-168 to indicate a presumptive requirement for *in vivo* toxicology studies unless otherwise justified, and where "**If the outcome of steps 1 and 2 ~~raises concerns, the need for comparative in vivo studies should be decided case-by-case~~ suggests that in vivo studies may not be necessary, the decision to waive in vivo studies should nevertheless be decided on a case-by-case basis in consultation with regulatory authorities**."	Partly accepted. The acceptance of clinical trials is the responsibility of the member states. Moreover, scientific advice cannot be required. The following sentence is added in lines 206-207: 'If a relevant in vivo animal model is not available the sponsor may choose to proceed to human studies taking into account principles to mitigate any potential risk.'
165-166	21	**Comment:** It should be clarified what type of data from the *in vitro* studies would provide a scientific justification that safety testing is not necessary for a mAb	Post-translational modifications may influence immunogenicity, but it seems highly unlikely that unexpected biological activity may be ascribed to them. Moreover, the limitations of an *in vivo* study (such as sensitivity and variability) to pick this up should be taken into account.

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		The impact of differences in post-translational modifications on nonspecific binding, biodistribution and thus PK cannot be reasonably addressed by the experiments described. The step 2 parameters do not sufficiently address safety - particularly for products with narrow therapeutic indexes. If posttranslational modifications are significantly different from innovator drug (the innovator may be the only one with the data that puts the significance into perspective) there is potential for off target toxicity, or changes in existing toxicity profiles. **Proposed change (if any):** Include requirement for comparative nonclinical study, particularly in cases where therapeutic index is small to minimize risk to human study population.	The aspect of post-translational modifications is currently being addressed in the revision of the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues'. If the similarity exercise indicates that the biosimilar and the reference mAb cannot be considered biosimilar, it may be more appropriate to consider developing the product as a stand alone.
165-170	14	vivo studies and their nature should be made on a case-by-case basis taking into account the results of the comparative physicochemical and biological testing, the availability of appropriate models and the potential of the in vivo studies to generate meaningful data. If the rigorous comparative physicochemical and biological testing and an array of in-vitro tests demonstrate sufficient comparability between the biosimilar and the reference product, in vivo studies in animals should not be required.	Comment noted.

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		Our experience has shown that a battery of comparative in-vitro pharmacodynamic studies is most suitable to measure e.g. differences in bioactivity because these assays are typically much more sensitive and specific than in vivo studies. If animal studies are considered necessary after such in-vitro studies, in the interest of animal welfare, repeat dose toxicity studies in pharmacologically responsive rodents should be considered rather than performing studies in non-human primates. Proposed change: No changes are recommended	
165-194	7	Comment: It is recommended that a statement is added to the guideline clarifying that *in vivo* non-clinical evaluation should be a default expectation unless the sponsor can justify the absence. The guideline should clarify that any intention to omit *in vivo* studies, prior to human exposure, requires scientific advice to confirm the acceptability of such an approach.	This is the same comment as comment lines 164-194 from stakeholder 5. Partly accepted. The acceptance of clinical trials is the responsibility of the member states. Moreover, scientific advice cannot be required. The following sentence is added in lines 206-207: 'If a relevant in vivo animal model is not available the sponsor may choose to proceed to human studies taking into account principles to mitigate any potential risk.
167	20	Comment: "…If the outcome of steps 1 and 2 raises concerns, the need for comparative *in vivo* studies should decided case-by-case."	Partly accepted. The section on the determination of the need for in vivo studies has been rewritten to make it clearer in which situations an in vivo study would be deemed necessary.

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		Who is expected to decide about this? The biosimilar company, the competent authority responsible for the clinical trials, or is the applicant recommended to contact CHMP? To our understanding there are always some concerns, and consequently, animal studies should be carried out prior to clinical studies. Proposed change: Please provide requested clarifications.	
167	21	**Comment:** "…If the outcome of steps 1 and 2 raises concerns, the need for comparative *in vivo* studies should decided case-by-case." Who is expected to decide about this? The biosimilar company, the competent authority responsible for the clinical trials, or is the applicant recommended to contact CHMP? To our understanding there are always some concerns, and consequently, animal studies should be carried out prior to clinical studies. **Proposed change (if any):** Please clarify	Please refer to the comment above.

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169-172	22	**Comment:** This section appears to emphasize that animal PK data would be considered the necessary component of any *in vivo* program, with the inclusion of safety and PD endpoints as optional elements. This emphasis on comparative PK is not fully described or justified as specifically relevant to MAbs. Existing guidelines emphasize a comparison of pharmacology (PD) and toxicity (safety) with PK included in the context of toxicokinetics. Comparative PK in animals is not emphasized as a requirement for non-clinical biosimilarity evaluations. We recommend placing the emphasis on toxicology and PD. **Proposed Change:** We suggest the alternative text, "the focus of the study (**safety, PD and/or PK**)…" Animal studies should be designed to maximize the information obtained **and PK or PD endpoints may be included in a safety study, such as to evaluate toxicokinetics, if considered appropriate and feasible.**"	Not accepted. Toxicity of mAbs is usually linked to exaggerated pharmacology. Rare examples of unexpected toxicity are known during development of novel MAbs. However, unexpected toxicity has not been reported after a manufacturing change of an innovator MAb and is therefore not anticipated to be associated with biosimilar mAbs that are considered similar to the reference mAb on a physicochemical and in vitro functional level. If an in vivo study is needed, the focus of the study could be PK and/or PD and/or safety. Safety does not refer to a classical toxicology study here, but is intended as clinical safety observations.
173	17	Comment: *In vivo* studies, when conducted comparatively, also give the opportunity to gain valuable insight into potential differences in immunogenicity between the biosimilar and the reference drug.	Not accepted. There is no need to add another paragraph on immunogenicity. Immunogenicity is already addressed further down in the guideline and highlights the value of immunogenicity assessment for interpretation of animal studies. This section is maintained as was proposed in the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Add after line 173: **"*In vivo* studies, when conducted comparatively, also give the opportunity to gain valuable insight into potential differences in immunogenicity between the biosimilar and the reference drug."**	draft guideline.
173 - 177	2	Comment: Relevant animal species is imprecise, in general that would be a non-human primate (as stated later) Proposed change (if any): Delete "availability of a relevant animal species"	Not accepted. If the concern is PK, it does not need to be a non-human primate.
173-177	11	Comment: With respect to comparative PK and PD studies, we support the suggestion of quantitative comparison for both PK and PD, when possible, of biosimilar and reference products in pharmacologically relevant models. We also agree with the recommendation for dose-response assessment covering a therapeutic dose in humans, especially for a PD study. However, in cases where PD readout or PD relevant models are not available, and there is a need to conduct a PK comparability study, we ask that a statement indicating that one dose level at an efficacious dose be sufficient for PK comparison purposes in most cases, providing	Not accepted. It is not clear why a non-clinical PK study would need to be reduced to the minimum if this study is meant to investigate a PK concern.

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		scientifically supportive justifications, in concurrence with the agency's recommendation for clinical PK study (lines 225-227).	
175	17	Comment: Section 4.3 (lines 178 and following) basically allows to perform non-comparative *in vivo*-tox studies if scientifically justified. Proposed change: "Such model would **ideally** 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."	Agreed. The wordings have been changed to "When the model allows, …".
175-177	1	Comment: When referring to PK/PD comparability studies in rodent models (e.g. xenografts, transgenics), it doesn't make sense to include clinically relevant doses. The tumour burden in the xenografts or expression levels in transgenics is so much higher compared to what is seen in disease, that clinical doses are not effective. Proposed change (if any): Delete this sentence (starting at "including dose response…") and replace with: "A well defined, homogeneous model may provide useful complementary data to the structure / function in	Partly accepted. It is agreed that the proposed sentence is general and for certain animal models therapeutic doses may not be effective. However, "covering a therapeutic dose" does not exclude the incorporation of higher dose groups as well. The proposed change does not address the issue of quantitative comparisons.

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		vitro assays to support in vivo justification for differences seen when individual attributes are assessed in vitro.”	
175-177	20	Comment: “…performing *in vivo* comparative PK and PD studies…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.” Proposed change: It is well accepted that *in vivo* comparative PK/PD studies help establish the PK/PD similarities in animals, and provide some confidence on biosimilars to be further confirmed in clinical studies. However, it is important to point out that Safety and PD endpoints, and similarity in animals cannot replace comparative human studies. So the similarity in animals should be viewed as a pre-requisite requirement. Most mAbs cross-react with primates. In this case the PK comparability study in NHP shall be mandatory/strongly recommended. The PK assay should be antigen-specific and fully validated and as close as possible to the assay used for the original drug. A study design should be adequate to fully characterize	This is a general comment and not a proposed change.

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		the PK profiles, especially in the presence of "antigen sink" effect. Monitoring of PD is strongly recommended as the mAb may induce different PD at the same exposure level.	
175-177	21	**Comment:** "…performing in-vivo comparative PK and PD studies…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." **Proposed change (if any):** It is agreed that *in vivo* comparative PK/PD studies help establish the PK/PD similarities in animals, and provide some confidence on biosimilars to be further confirmed in clinical studies. However, it is important to point out that Safety and PD endpoints, and similarity in animals cannot replace comparative human studies. So the similarity in animals should be viewed as a pre-requisite requirement.	Please refer to the comment above.
177	7	Comment: Due to likely differences in exposure across species (from animals to humans) at a particular dose, the use of "dose" as a reference to relate the "exposure" from animals to humans is less appropriate than using "concentration" or "exposure" as a reference.	Accepted. The text has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "…, including dose**-concentration**-response assessment covering a therapeutic dose **and/or exposure** in humans."	
177	17	Comment: When referring to PK/PD comparability studies in rodent models (e.g. xenografts, transgenics), it doesn't make sense to include clinically relevant doses. The tumor burden in the xenografts or expression levels in transgenics are so much higher compared to what is seen in disease, that clinical doses are not effective. Proposed change: It is suggested to delete this (starting at "including dose response…") and replace with: **"A well defined, homogeneous model may provide useful complementary data to the structure / function *in vitro* assays to support *in vivo* justification for differences seen when individual attributes are assessed *in vitro*."**	This is the same comment as lines 175-177 from stakeholder 1. Partly accepted. It is agreed that the proposed sentence is general and for certain animal models therapeutic doses may not be effective. However, "covering a therapeutic dose" does not exclude the incorporation of higher dose groups as well. The proposed change does not address the issue of quantitative comparisons.
177	22	**Comment:** Due to likely differences in exposure across species (from animals to humans) at a particular dose, the use of "dose" as a reference to relate the "exposure" from animals to humans is less appropriate than using "concentration" or "exposure" as a reference.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: We suggest that the phrase "dose-response" should be expanded to be "**dose-concentration-response**" and "covering therapeutic dose in humans" should be expanded to "**covering therapeutic dose and/or exposure in humans**."	
178	7	Comment: It is recommended that if no relevant species exist, a limited toxicology assessment is still required before the biosimilar mAb is given to humans and that biosimilar applicants should consider using the species employed by the innovator company during development of the reference product.	Not accepted. This is not in accordance with the recommendations given in the ICHS6 addendum, where in such cases risk mitigation strategies are recommended.
178 - 184	4	Comment: The assumption here is that NHP have a predictive value in these type of studies. On which data is this assumption based?	Accepted. The guideline is now clearly stating that 'The conduct of toxicological studies in non-human primates is not recommended. Also, the conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended.'
179-182	20	Comment: "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,	Not accepted. An *in vivo* study should not be requested as a default (see similar comments above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		unless scientific justification can be provided to indicate that a direct comparison is unnecessary.” Prior to entry into human, nonclinical studies should be designed and powered to identify differences in PK, and dose-response relationship of adverse findings. It should be clarified whether “use of one dose” means one dose level (with repeated administration) or a single dose study. We do not think that a single dose study in one gender would be sufficient to assess safety. In addition, use of only one gender is not always appropriate and would need to be scientifically justified. Proposed change: An appropriately designed (in order to understand the dose-response relationship) nonclinical PK/PD study with safety endpoints should be conducted to clearly identify differences in PK/PD and toxicity profile. The result of this in vivo nonclinical evaluation forms the basis for determining the extent and nature of additional nonclinical testing to be performed.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
179-183	21	**Comment:** "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." As outlined in the "General comments on Non-clinical studies" above, comparative toxicology studies should be mandatory to safeguard patients included in clinical trials/prior to FIM administration. They should be as small as reasonably justifiable. **Proposed change (if any):**	Not accepted. A comparative toxicology study should not be requested as a default (Please see similar comments above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
180-184	11	Comment: We support the recommendation that "if *in vivo* safety testing is needed in non-human primates, the use of only one dose and one gender and omission of a recovery group might be justified". However, we believe that this approach should be considered a standard and as such clearly stated in the guidance. Proposed change (if any): Please consider changing the sentence to: "If *in vivo* safety testing is needed in non-human primates, the use of only one dose and one gender and omission of a recovery group is generally acceptable, as a standard approach".	Not accepted. The guideline is now clearly stating that 'The conduct of toxicological studies in non-human primates is not recommended. Also, the conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended.'

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
180	21	**Comment:** Prior to entry into human, nonclinical studies should be designed and powered to identify differences in PK, and dose-response relationship of adverse findings. **Proposed change (if any):** An appropriately designed (in order to understand the dose-response relationship) nonclinical PK/PD study with safety endpoints should be conducted to clearly identify differences in PK/PD and toxicity profile. The result of this in-vivo nonclinical evaluation forms the basis for determining the extent and nature of additional non-clinical testing to be performed.	Not accepted. It is not clear why an *in vivo* animal PK (and PD) should be performed as a default. Rather, only if a certain question needs to be investigated, an in vivo study needs to be performed. If an in vivo study is needed, the focus of the study could be PK and/or PD and/or safety. Safety does not refer to a classical toxicology study here, but is intended as clinical safety observations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
180-181	21	**Comment:** "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." It is not clear whether "use of one dose" means one dose level (with repeated administration) or a single dose study. We do not think that a single dose study in one gender would be sufficient to assess safety. Moreover, it is not clear how the dose level or study duration would be selected if only one dose can be selected for a study and no PK and/or toxicity data are available for the reference molecule. In addition, use of only one gender is not always appropriate and would need to be scientifically justified. **Proposed change (if any):** Additional guidance on additional studies is needed.	Not accepted. The guideline is now clearly stating that 'The conduct of toxicological studies in non-human primates is not recommended. Also, the conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended.'

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
181 - 183	4	Comment: It is stated that the toxicology study in principle, should be comparative. However, in the preceding lines, it is mentioned that NHP is usually the relevant species, but that large comparative studies in these species are not recommended. We agree that large comparative studies should not be undertaken, but small comparative studies are not useful as the small number will make it impossible to make real comparisons. Furthermore, toxicity of monoclonal antibodies is related to exaggerated pharmacology (covered by *in vitro* data) and off-target toxicity is unlikely. Hypersensitivity reactions could be an issue, but again, a small study in NHP is unlikely to be predictive in this respect. We propose to delete the requirement to have the toxicology study be comparative in nature. Proposed change (if any): The following sentence should be deleted: *In principle, the toxicology study should be comparative in nature, unless scientific justification can be provided to indicate that a direct comparison is unnecessary.*	Accepted. The sentence is removed. Moreover, it is no longer recommended to conduct toxicological studies in non-human primates nor in non-relevant species in the frame of a biosimilarity excercise.
181-183	17	Comment: This sentence is in contradiction to previous paragraphs and the guideline on non-clinical and clinical issues section 4.1 where comparative studies are required. If in-vivo studies will be required they should always be	Not accepted. It is not recommended to conduct toxicological studies in non-human primates nor in non-relevant species in the frame of a biosimilarity excercise. Toxicity of mAbs is usually linked to exaggerated

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		comparative and it seems highly unlikely that there is any scientific justification which would suggest that a direct comparison is unnecessary. Proposed change: ~~In principle, the toxicology study should be comparative in nature, unless scientific justification can be provided to indicate that a direct comparison is unnecessary.~~	pharmacology. Rare examples of unexpected toxicity are known during development of novel mAbs. However, unexpected toxicity has not been reported after a manufacturing change of an innovator MAb and is therefore not anticipated to be associated with biosimilar mAbs that are considered similar to the reference mAb on a physicochemical and in vitro functional level. If an in vivo study is needed, the focus of a comparative study could be PK and/or PD and/or safety. Safety does not refer to a classical toxicology study here, but is intended as clinical safety observations.
185-186	20	Comment: The guideline does not address how impurities have to be qualified if they exceed the qualification threshold according to ICH Q3 for the biosimilar drug product. It is not clear why, for example, an e.g., organic impurity cannot be tested in a rodent study. If rodent as a non-responder is not acceptable would then the monkey study be required? Proposed change: Further clarification is required.	Not accepted. This issue will be addressed in the revision of the general quality guidance for biosimilars 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues'. Qualitative differences (i.e. presence or absence of product-related substances and/or impurities) require a thorough justification, which may include non-clinical and/or clinical data, as appropriate. It is however preferable to rely on purification processes to remove impurities rather than to establish a non-clinical testing program for their qualification. (The latter is taken directly from ICHS6).
185-186	22	**Comment:** This message by itself could be interpreted differently, particularly when no relevant species exists or when there is no relevant PD marker.	Not accepted. The proposal does not follow ICH S6 guidance. The guideline now states the following:

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		Proposed Change: We suggest the alternative text, "In the absence of appropriate cross-reactivity in a nonhuman species, the biosimilar candidate should be assessed by other means that will ensure the product can be safely administered to humans."	'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 of concern do not block direct entrance into humans, an *in vivo* animal study is not considered necessary….. If a relevant in vivo animal model is not available the sponsor may choose to proceed to human studies taking into account principles to mitigate any potential risk.' It is obvious that in case the similarity exercise indicates that the biosimilar and the reference mAb cannot be considered biosimilar, it either may be more appropriate to consider a stand alone development, or the development would need to be stopped.
185-186	21	**Comment:** The guideline does not address how impurities have to be qualified if they exceed the qualification threshold according to ICH Q3 for the biosimilar drug product. It is not clear why, for example, an e.g. organic impurity cannot be tested in a rodent study. If rodent as a non-responder is not acceptable would then the monkey study be required ? **Proposed change (if any):** Further clarification required	Same comment as lines 185-196 from stakeholder 20. Please see comment above.

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190-191	17	Comment: It is surprising that local tolerance endpoints should only be included if there is a special need for additional information. If in-vivo testing will be considered necessary, observing local tolerance should be part of the standard evaluation of toxicological studies. Therefore, the sentence should be deleted as not relevant. Proposed change: "~~Local tolerance endpoints should only be included in an *in vivo* study if there is a special need for additional information.~~"	Accepted. The sentence has been removed. Separate local tolerance studies are not required.
192	21	**Comment:** What if subtle differences in toxicity profiles are observed? There is no discussion on what impact this will have on the *in vivo* toxicity package needed for the similar biological product. Will additional toxicity evaluation be needed (larger comparative general toxicity studies, repro toxicity etc)? The critical attributes that can impact in utero exposure in early gestation are poorly understood. It may be premature to recommend no need for repro studies in all cases **Proposed change (if any):**	Not accepted. Toxicity of mAbs is usually linked to exaggerated pharmacology. Rare examples of unexpected toxicity are known during development of novel mAbs, but have not included reproductive toxicity.

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192-194	4	Comment: What is " not routine requirements"? Proposed change (if any): These studies are not required	Accepted.
192 - 194	5	Comment: The draft guideline states that safety pharmacology, reproduction toxicology, mutagenicity, and carcinogenicity studies are not routinely required. We agree that in many cases they will not be needed, but we believe it would be more appropriate to state in the guideline that this decision must be made on a case-by-case basis based on the known and potential risks of the compound. Proposed change (if any): ~~"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.~~ **Although safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies will not ordinarily be necessary for biosimilar mAbs, whether they will**	Not accepted. If there would be doubts regarding any of these, the product would not be approved as a biosimilar.

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		be required for a particular mAb biosimilar will be a case-by-case assessment and will depend on a variety of factors."	
192-194	7	Comment: The studies listed as 'not routinely required' may be necessary if the biosimilar product poses a risk due to the presence of non-active substance, such as formulation components, product or process related impurities etc, that are not known. Proposed change: The guideline should be more explicit about the potential risk factors affecting the need for such studies.	Please see above for issues on factors triggering the need for *in vivo* studies.
192-194	22	**Comment:** These data may be necessary if the biosimilar product is at risk for the list of toxicity due to non-active substance, such as formulation components, product or process related impurities that are unknown.	Please see comment above.

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		It should be acknowledged that such factors would not justify use of higher species such as non-human primates. **Proposed Change:** We suggest that the text should be more explicit about the potential risk factors that may drive requirements for additional toxicology studies.	
195	17	Comment: For applicants striving for a global biosimilar development, clinical data generated with a reference medicinal product sourced from another ICH region (e.g. US, JP) might be desirable and also acceptable as long as this product is approved based on a full quality, safety and efficacy data package and as long as this product is indistinguishable from the corresponding EU reference medicinal product with regard to quality, safety and efficacy. Besides demonstrating comparability on the physico-chemical and biological level it might even be considered in certain cases to provide comparative PK data between the biosimilar and the reference products from the other ICH region. Proposed change: please add after line 195 as introductory part to the section "Clinical studies": **"According to the Guideline on Similar Biological Medicinal Products (CHMP/437/04) the chosen reference medicinal product, defined on the basis**	While BMWP agrees that the issue of global biosimilar development is of importance, BMWP will at the current stage not include any wording on this aspect since this has to be considered in the framework of a general biosimilar development.

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		of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies. However, on a case-by-case basis the use of the reference medicinal product authorised in the European Community instead of the reference product authorised in another ICH region (e.g. USA or Japan) might be possible for certain safety and efficacy studies, provided the reference product from that other region is equivalent to the corresponding EU reference product with regards to physico-chemical and biological parameters. In such cases Sponsors are recommended to seek scientific advice from the European Medicines Agency before starting the clinical trials."	
196	17	Comment: Although biosimilar clinical development programs usually follow a stepwise approach, i.e. comparative PK studies precede the comparative efficacy and safety trials, for biosimilar mAbs such sequential arrangement requiring PK data before entering phase III clinical trials may be proved unnecessary. Provided that quality and non-clinical data already support biosimilarity of test and reference product, conducting comparative PK studies in patients (where the study population receives the therapeutic doses and treatment regimen just like in the case of comparative efficacy trials) parallel with and not prior to pivotal efficacy and safety trials would	Accepted. This is covered in the clinical part of the guideline.

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		not pose additional risk for the patients involved in the latter studies. Furthermore, the most sensitive patient population of the comparative PK and efficacy/safety study might be the same, the only difference in the two clinical trial settings would only be the main objectives of the studies (i.e. the primary and secondary endpoints would be determined differently). Therefore the reason why the comparative PK data should be provided prior to the start of the efficacy trials seems to lack substantial support. Knowing the fact that in the case of mAbs the PK parameters show high variability, besides the study durations even the study size would be comparable for these clinical trials. Alternatively, if needed, some preliminary PK supportive data could be provided by *in vivo* animal studies or PK data could be monitored during the comparative PK study by setting up a data safety monitoring board to evaluate interim data while keeping the integrity of the trial.	
196	20	Comment: More specific recommendations regarding the use of assays for measurement of antibodies (type of assay, sensitivity, measurement of function, concentration) are needed. For clarity the final mAb biosimilar guidance should cross-reference the antibody immunogenicity guidance, since the "standard" immunogenicity assessment techniques are suitable for the comparative exercise conducted in biosimilar development. Proposed change:	Accepted (Please see section 5.4, clinical safety).

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		Cross reference to other relevant guidance documents	
196-299 197-207	20	An appropriate introduction should be included, similar to the introduction to the non-clinical section, overall stating the approach to be followed.	Accepted. A statement has been added.
196-423 260-279	14	Comment: Provided analytical comparability demonstrates that the biosimilar product attributes fall within the variability of the reference product, biosimilarity can be demonstrated by human testing. In case a predictive PD marker as surrogate for clinical efficacy is available and comparative PK has demonstrated that there are no meaningful differences between the biosimilar and the reference mAb, it should be sufficient to conduct comparative PK/PD studies to demonstrate biosimilarity for approval. In such cases, a formal phase III trial should not be necessary as safety and efficacy are extrapolated from the originator reference product. Where feasible, concomitant safety evaluation should be done, e.g. in a non-comparative phase III trial to confirm that the safety profile is comparable to published literature referring to the reference product. However, rare immunogenic reactions are unlikely to be detected pre-approval. In addition, as seen for biologics in the past such rare reactions are related rather to the	Accepted (Please see section 5.3, clinical efficacy).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drug product than to the drug substance. As such issues cannot be excluded for biosimilars nor for biologics upon manufacturing changes in general, we support the risk management plans as currently applied for all biologics. In case available PD markers are not predictive of clinical efficacy in a relevant indication, we would consider the necessity for a phase III study. However, in this scenario the sequence of the clinical studies should be flexible. Based on the high physicochemical and biological similarity and after PK/PD comparability has been demonstrated, it is not to be expected that the biosimilar and originator mAB behave differently in the indications for which the originator was approved. The sponsor could therefore elect to perform concurrent phase I and phase III trials or a phase I/III trial as the same efficacy and safety results would be anticipated. In this case the sponsor is accepting the risk of accelerating the program based on solid scientific data and patient safety is not compromised. The more the biosimilar product deviates from the variability of product attributes of the reference product, the greater evidence is required to move into the clinic, as well as to demonstrate overall biosimilarity. Proposed change : No changes are recommended	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
198-199	11	Comment: We agree that comparison of PK properties of biosimilar and innovator mAbs is an essential part of biosimilar development. Demonstrating the clinical pharmacokinetic similarity of a biosimilar is a critical first step to demonstrate that it will behave similarly to the innovator molecule in the clinic and provides a strong basis for proceeding with development.	Accepted.
198-199 214-215	20	Comment: We agree that comparison of PK properties of biosimilar and innovator biologic molecules is an important part of biosimilar development. Demonstrating the clinical pharmacokinetic similarity of a biosimilar is the first step to demonstrate that it will behave similarly to the innovator molecule in the clinic. However, single dose PK studies in healthy volunteers and/or patients have limited utility in establishing similarity of a biosimilar to the reference product, as pharmacokinetics can change with time due to many factors i.e. immunogenicity, tumour burden etc. In most cases, the utility of single dose studies is to provide the initial clinical data that support moving forward with multiple dose PK studies, PK/PD studies or efficacy/safety studies in patients.	It is considered that a single dose PK study, if possible in healthy volunteers, is the most sensitive design to compare the PK behaviour of the biosimilar and reference products due to high variability in patients due to numerous factors.
199	1	Comment: typo	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "..forms.."	
199	17	Comment: „A parallel group design is acceptable due to the long half-life of monoclonal antibodies and the potential influence of immunogenicity." In many cases of biosimilar developments cross-over design was applied before. Although most mAbs have long half life not making them suitable for cross-over design the below modification is suggested: **Proposed change :** **„<u>Besides a cross-over design</u>,** ~~A~~ a parallel group design is acceptable due to the long half-life of monoclonal antibodies and the potential influence of immunogenicity."	Accepted. The whole paragraph on study design has been revised.
199-200	11	Comment: A parallel design might not always be needed, especially for products with no or low immunogenicity. In addition, the cross over design could also give some information on moving from one product to another. For instance, etanercept has such a low incidence of neutralizing antibodies that a cross over design would be appropriate. For drugs like adalimumab, where the ADA levels might be 10-20% depending on population,	Accepted. The whole paragraph on study design has been revised.

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		this could be dealt with by replacement in a cross over design. Proposed change (if any): Cross over designs should be allowed as suitable, depending on the drug and the clinical situation.	
199-201	22	Comment: The guidance recognizes that the pharmacokinetics of mAbs are different than therapeutic proteins and small molecule drugs; it specifically states that parallel group designs are acceptable due to the longer half-lives of mAbs. However, as cross-over pharmacokinetic studies are internationally recognized as the preferred norm due to reducing subject PK variability ("each subject is his/her own control") more guidance should be given as to which situations truly warrant a parallel pharmacokinetic study. Care should be taken that this parallel approach is only taken after careful exploration of a cross-over PK design.	
200	2	Comment: Acceptable is too weak Proposed change (if any): Replace acceptable by recommended	Not accepted. When possible, cross-over is considered the most sensitive design.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
200	2	Comment: It should be stated what a single dose study in healthy volunteers may be used for Proposed change (if any): Single dose bioequivalence studies may be possible	Accepted. The whole paragraph on study design has been revised.
200	3	Comment: using the word "acceptable" (in "A parallel group design is acceptable…") does not seem strong enough. Proposed change (if any): "A parallel group design is *necessary*…"	Not accepted. When possible, cross-over is considered the most sensitive design.
200	21	**Comment:** using the word "acceptable" (in "A parallel group design is acceptable…") does not seem strong enough. **Proposed change (if any):** "A parallel group design is usually necessary	Not accepted. When possible, cross-over is considered the most sensitive design.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
201-203 214-215 235-242	21	**Comment:** While single dose PK evaluation may indeed be most sensitive, clearance and other parameters may change after first dose, hence a single dose evaluation will not correctly describe the true profile in the context of safety/tolerability and therapeutic response of a biosimilar. For the evaluation of biosimilars to anticancer mAbs single dose studies are unlikely to describe the PK profile sufficiently because such trials can normally not be conducted in healthy volunteers and clinical efficacy cannot be established. In such situations to most appropriate study will be a multidose PK evaluation after 1st dose and at steady state as stated in 5.1.3. **Proposed change (if any):** It seems advisable to clarify preconditions for single and multidose PK studies dependent on the PK characteristics of the mAbs. For mAbs with non-linear PK, dose-ranging single-dose comparisons would be necessary. For antibodies with time-dependent PK, dose-ranging multiple-dose PK comparisons would be necessary.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
201-207	20	Comment: While single dose PK evaluation may indeed be most sensitive, clearance and other parameters may change after first dose due to immunogenicity, disease progression etc., hence a single dose evaluation will not correctly describe the true profile in the context of safety/tolerability and therapeutic response of a biosimilar. For the evaluation of biosimilars to anticancer mAbs single dose studies may not describe the PK profile sufficiently, particularly where an antigen is directly expressed on the tumour, thus antigen load will be dependent on tumour load In such situations the most appropriate study will be a multidose PK evaluation after 1st dose and at steady state as stated in 5.1.3. In this case, the PK might most effectively be studied using population PK as part of a therapeutic trial It seems advisable to clarify preconditions for single and multidose PK studies dependent on the PK characteristics of the mAbs. For mAbs with non-linear PK, dose-ranging single-dose comparisons would be necessary. For antibodies with time-dependent or disease dependent PK, dose-ranging multiple-dose PK comparisons would be necessary. Proposed change: "In many cases, in principle, a single dose PK evaluation is most sensitive and data from such studies	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be provided. However, for the design of a PK study for a biosimilar mAb, particulars like the clinica Ccntext will have to be taken into account. For mAbs that are intended to be dosed more than once, Applicants should conduct a multi-dose PK study in the appropriate patient population. For cases where PK is nonlinear, time–dependent and/or dependent on disease state (e.g. where antigen is expressed directly on a tumour) pharmacokinetic studies utilizing a range of doses and/or at steady state are required to assess biosimilarity. In some cases population PK may be the most effective way to describe the PK characteristics of the mAb, and this may be best achieved as part of a therapeutic trial.	
202-204	21	**Comment:** "…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…" Single dose PK similarity is important, but may not be sufficient in order to claim PK similarity. It is possible that mAbs show nonlinear and time-dependent PK which cannot be evaluated with a single dose PK study at a single dose level. Thus, the PK similarity claim in the product information should be solely based on and limited to results from well designed head-to-head comparison(s).	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		If the reference mAb is dosed with titration, or strong PK covariates (e.g., disease status, target expression) have been identified, it may be clinically relevant to compare PK at different dose levels and assess the PK correlation with established covariates. PK data collected in larger efficacy/safety trials should be included the PK similarity claim. **Proposed change (if any):** PK data collected in larger efficacy/safety trials should be included the PK similarity claim.	
202-204	5	Comment: Section 5.1.1 of the guideline discusses PK study design. We agree in general with the points made and the observation that a single dose evaluation may be appropriately sensitive in many cases. We suggest that the guideline include more discussion of trial design for mAbs that are dosed more than once (whether consistently or intermittently, such as during flare ups). In our experience, the PK (specifically, the clearance) of some mAbs may change over time in individuals. We think this may be attributable in at least some cases to immunogenicity at very low (currently undetectable) levels. Whatever the explanation, this phenomenon demonstrates the importance of multi-dose PK studies.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A biosimilar mAb applicant should be able to establish what happens to the product's PK over time. Proposed change (if any): "In ~~such~~**some** 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.~~ **if a mAb is designed to be dosed more than once (including by intermittent dosing), the biosimilar applicant should design and complete an appropriate multi-dose parallel design study."**	
208-233	11	Comment: We agree with the concept that once biosimilarity has been established between biosimilar and innovator, the established properties of the innovator molecule (e.g. behavior in special populations, metabolic profile, etc.) can reasonably be considered to apply to the biosimilar molecule, when scientifically justifiable. In this spirit, we request that the agency add a sentence specifically addressing DDI studies to section 5.1.2. Proposed change (if any): Suggest adding "Drug-drug interactions studies are not normally required as the overall objective of the development program is to establish biosimiliarity. Once biosimilarity is established, the known DDI profile	Not accepted. It is not considered necessary to list in the guideline all the studies that are not required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of the innovator compound can reasonably be considered to apply to the biosimilar molecule."	
209-212	21	**Comment:** "…to show comparability in pharmacokinetics of the biosimilar with the reference product in a sufficiently sensitive and homogeneous population." • It remains unclear what "sufficiently sensitive and homogeneous population" means. The question is whether this should be replaced with the term, "relevant population." Relevance might include homogeneity and sensitivity, but there are also more clinical parameters. If a homogeneous population/sensitive population refers to a subgroup of patients from a pivotal study, then we would have concern that testing in such groups may not be validated as prospective, pre-specified studies have often not been performed for such subgroups and the results may, therefore, be misleading. Lines 218-227 provide factors that may influence the PK, but this does not help select a sensitive population to potential PK differences. In addition, since the goal is to establish the PK similarity, dose and time dependency have to be established rather than optional because higher or lower exposures dosing could result in efficacy and/or safety concerns. Different doses	Not accepted. The "most relevant population" is not considered a clearer and more informative wording. The sensitivity of the population has to be justified by the Applicant and it is not possible to be more specific in a general guideline. Homogeneity is recommended in order to decrease the number of patients needed and the risk of imbalanced treatment groups.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be tested especially when dose titration or multiple dose levels are used clinically for the reference mAb. In case dose modification for special populations is listed in the reference mAb label based on PK covariates, the biosimilar mAb PK should be thoroughly investigated and the same dose modification label should not be copied without sufficient data support. **Proposed change (if any):** Please clarify what factors define a sensitive and homogeneous population for PK evaluation. Line of therapy should be added as an example of efficacy patient population. Efficacy studies are needed despite *in vitro* and *in vivo* PK similarity studies.	It is unclear how this relates to the topic.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
209-212 239-240 254-256	13	209 The primary objective of the pharmacokinetic studies performed to support a Marketing Authorisation 210 Application (MAA) for a similar biological medicinal product is to show comparability in 211 pharmacokinetics of the biosimilar with the reference product in a sufficiently sensitive and 212 homogeneous population. 239 clearance and half-life should be determined and reported in a descriptive manner. If relevant 240 differences occur the assumption of similar PK might be seriously questioned. If such results are As a principle, any 254 widening of the conventional equivalence margin beyond 80-125% requires thorough justification, 255 including an estimation of potential impact on clinical efficacy and safety. This should be discussed with 256 regulatory authorities. Comment: For the clinical aspects the same point raised in [(1)] is valid. 1.) Assuming the Biosimilar needs to be as safe and effective as the Reference Medicinal Product as indicated in lines: 209 to 212 and that the clinical	Not accepted. This is not specific to mAbs and will be addressed in the revision of the general Non-clinical and Clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		efficacy of the Biosimilar is required to be similar to the Reference Medicinal Product. 2.) The PK studies require to be similar compared to the Reference Medicinal Product. Referring to lines: 239 and 240 3.) Taken also lines: 254 to 256 into account, clearly the safety and efficacy comparability exercise is subject to tolerance margins. However this margin of tolerance is not clear and would require further elucidation. What is the justification for a "generally acceptable" margin with regard to Biosimilars? Taken into consideration the following points: 1.) the problems associated with populations for trials for example in a cancer setting where sufficiently homogenous population might be rare and healthy volunteers cannot be used for ethical reasons either. 2.) cases where the "Quality Profile" of the Reference Medicinal Product exceeds already an efficacy margin of 80-125% when compared on a batch to batch basis in clinical trial to itself. There is also additional clarification required, from the innovator industries point of view, mainly on the following points: 1.) Taken the costs associated with clinical trials into account and the need to reduce healthcare costs, is it	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		required to assess multiple batches of the Reference Medicinal Product when comparing it with the Biosimilar in a clinical trial setting, as a general question? 2.) As indicated in lines: 209 to 212 the expectation is that safety and efficacy are "comparable". A) Does this mean the acceptable tolerance margin for the Biosimilar in a clinical efficacy trial is required to be within the variation of endpoints of multiple batches of the Reference Medicinal Product and then the conventional equivalence margin of 80%-125% for the Biosimilar is appicable? Or B) Does this mean the acceptable tolerance margin for the Biosimilar in a clinical efficacy trial is based on one batch the Reference Medicinal Product and then the conventional equivalence margin of 80-125% for the Biosimilar is applicable? Proposed change (if any): None, i.e. clarification required. 424 6. Extrapolation of Indications 425 Extrapolation of clinical efficacy and safety data to	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		other indications of the reference mAb, not 426 specifically studied during the clinical development of the biosimilar mAb, is possible based on the 427 overall evidence of biosimilarity provided from the comparability exercise and with adequate 428 justification. Comment: Referring to lines 424 to 428, what would the justification be? As the mechanism of action of the Reference Medicinal Product could be different from indication to indication, is it justified to allow "Extrapolation of Indications" without showing the efficacy for this particular indication for the Biosimilar? For example for some indication an mAb might bind to a cell surface, whereas in other indications the primary action is to bind to soluble antigen. The subsequent clearance and inactivation mechanism might be very different. The EMA wrote on this topic the following: 1.) *2 EMA/CHMP/BMWP/86289/2010* *3 Committee for Medicinal Products for Human Use (CHMP)* *4 Guideline on immunogenicity assessment of monoclonal*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		5 antibodies intended for in vivo clinical use. *6 Draft* *"261 MAbs exert their action by various mechanisms ranging from simple binding to antigen, which alone* *262 mediates the clinical effect, to binding antigen and mediating one or more immunobiological* *263 mechanisms which combine to produce the overall clinical response. Therefore, although simple* *264 binding may seem to be the only mechanism operating to achieve clinical efficacy, other effects may* *265 also play a role in this."* *And* *"the mode of action of the mAb (e.g., lytic, apoptotic), and especially the nature of* *331 the target molecule (e.g., immunosilencing, immunostimulating), needs to be adequately characterized* *332 and comprehensively investigated"* Differences in the glycosylation pattern for example between the Reference Medicinal Product and Biosimilar could be for one mechanism of action negligible, whereas for another mechanism of action very important. The mechanism of action can be different	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		from indication to indication. As the mechanism of action can be influenced by the glycosylation pattern, which can be influenced by the "Quality Profile" (refer to "overlaying issue of product heterogeneity and variation [(1)]"); an important consequence of this train of thoughts is that new clinical efficacy data would be required for a new indication in order to ascertain that efficacy of the Biosimilar is comparable to the efficacy of the Reference Medicinal Product for this new indication (assuming the case of a different mechanism of action). Proposed change (if any): None, i.e. clarification required.	
209-213	15	Comment: We agree with the concepts voiced in this section of the draft guidance. Other than target-mediated effects (which could confound an assessment of product-inherent similarity, and therefore should be minimized), the factors that affect clearance of antibodies are generally similar among various indications.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
209-213	20	Comment: "…It remains unclear what "*sufficiently sensitive"* and *"homogeneous population*" means. The question is whether this should be replaced with the term, "relevant population." Relevance might include homogeneity and sensitivity, but there are also more clinical parameters. If a homogeneous population/sensitive population refers to a subgroup of patients from a pivotal study, then we would have concern that testing in such groups may not be validated as prospective, pre-specified studies have often not been performed for such subgroups and the results may, therefore, be misleading. Lines 218-227 provide factors that may influence the PK, but this does not help select a sensitive population to potential PK differences. In addition, since the goal is to establish the PK similarity, dose and time dependency have to be established rather than optional because higher or lower exposures dosing could result in efficacy and/or safety concerns. Different doses should be tested especially when dose titration or multiple dose levels are used clinically for the reference mAb. In case dose modification for special populations is listed in the reference mAb label based on PK covariates, the biosimilar mAb PK should be thoroughly investigated and the same dose modification label should not be copied without sufficient data support. Proposed change:	Not accepted. The "most relevant population" is not considered a clearer and more informative wording. The sensitivity of the population has to be justified by the Applicant and it is not possible to be more specific in a general guideline. Homogeneity is recommended in order to decrease the number of patients needed and the risk of imbalanced treatment groups.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please clarify what factors define a sensitive and homogeneous population for PK evaluation.	
212	8	Comment: The word homogenous population might be mis-leading and genomic stratification should be commented upon. Briefly, we feel that ultra-stratification of patients, for example in oncology, beyond the indications of the reference product should be discouraged. As an example, if a drug is licensed for EGFR+/wtKRAS metastatic colon carcinoma, it might not be appropriate to use a different genomic study population (for example EGFR+/wtKRAS, wtBRAF), unless that particular indication is sought. Indeed, there is no guarantee that the ultra-stratified population and the indicated population will respond similarly. We feel this point should be clarified. The expansion of genomic information, in particular in the field of oncology, would suggest that this will be a very important issue in the future.	Not accepted. Homogeneity of the population is recommended in order to decrease the number of patients needed and the risk of imbalanced treatment groups. However, it is not possible to be more specific in a general guideline and the selection of the population should be justified by the Applicant on a case-by-case basis depending on the data available for the reference product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): State that genomic/genetic homogeneity is intended as specified for the licensed indications of reference product and more stringent limitations are not encouraged.	
213	20	Comment: Guidance around the equivalence margins that are expected which should be 80-125 range. However, would suggest that this important discussion be a separate heading.	Accepted.
214	7	Comment: Clarification is requested on acceptable/expected PK endpoints (or PK parameters) to be monitored in single dose PK studies. It would be helpful to further clarify expectations for healthy volunteer studies (where similarity/differences can be most sensitively studied without confounders).	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
214-215	16	Comment: The current draft guideline does not propose a preferred primary endpoint for single dose PK studies. Proposed change (if any): For intravenous formulations, AUC (0-t) may be used as preferred primary endpoint in single dose PK studies as a measure of exposure. Half-life, Cmax ,Kel, Tmax, clearance and AUC0-∞ may be proposed as secondary endpoints in order to provide information on the pharmacokinetic comparison of the biosimilar versus the reference product.	Accepted. The revised version details the recommended PK endpoints.
214-215	20	Please see previous comments in lines 201-207.	Please see previous comment.
214-227	22	**Comment:** The text is lacking clarity on acceptable/expected PK endpoints (or PK parameters) to be monitored in single dose PK studies. Please address in similar fashion to section 5.1.3. **Proposed Change:** We suggest this clarity could be provided related to expected PK endpoints (*e.g.*, Cmax and AUC).	Accepted. The revised version details the recommended PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
214-227	22	**Comment:** There is no discussion of the potential risks associated with studying PK only in healthy volunteers (where similarity/differences can be most sensitively studied without confounders) prior to performing larger confirmatory studies in a disease population. **Proposed Change:** We suggest this section further clarify what expectations would be if healthy volunteer studies were undertaken, providing remarks on whether this would cause an increased risk in the disease population.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis.
215-218	21	**Comment:** "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… " We do not agree that PK similarity can be automatically extrapolated across indications even when the indications are related (i.e. in the same therapeutic area). Factors associated with different indications (e.g., dose and regimen, target expression, tumor burden, immunogenicity…) may impact the PK of reference and biosimilar mAbs differently. PK similarity needs to be established and extrapolation of PK similarity has to be justified on thorough understanding	Not accepted. The burden of the justification of extrapolation is on the Applicant on a case by case basis. If PK comparability is convincingly shown in the most sensitive population from a PK point of view, it is not expected that an additional PK study in a less sensitive population would provide any useful information.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of PK-disease interactions. **Proposed change (if any):** By default, PK similarity needs to be established for each indication. And it should be justified on a case-by-case basis if such a study is waived.	
215-227	20	Comment: The guideline states that it is not generally necessary to investigate the PK profile of different indications. EBE supports the principle that PK similarity and the ability to extrapolate must be considered on a case by case basis. It cannot be automatically assumed it is possible to extrapolate across indications, even when the indications are related (i.e. in the same therapeutic area). Factors associated with different indications (e.g., dose and regimen, target expression, tumour burden, immunogenicity…) may impact the PK of reference and biosimilar mAbs differently. PK similarity needs to be established and extrapolation of PK similarity has to be justified on thorough understanding of PK-disease interactions. Separate data for each indication may be needed 1) where mechanism of	Partly accepted. The proposed text on "relevant patient population" is considered unclear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		action may affect pharmacokinetics, 2) where indication is monotherapy or combination therapy or different concomitant medications, 3) different immune status of patients, 4) co morbidities, 5) susceptibility to adverse events, 6) route of administration or 7) dose. In each case the applicant should consider the different factors and scientifically justify why extrapolation is appropriate. The guideline suggests that applicants should focus on the population where PK equivalence may be studied with the most sensitivity. EBE supports this position and notes that population PK assessments may be the most sensitive manner to establish a PK profile, and these may be best effected in a therapeutic trial as a more sensitive and clinically realistic means, compared to separate PK studies. Proposed change (if any): "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. Applicants should consider whether the relevant patient populations differ with regard to route of administration, dose, mechanism of action, concomitant medications, co morbidities, and immune state. Separate PK studies may be needed as a support for extrapolation of clinical efficacy data between indications and the approach should be scientifically	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		justifiable. There may be more difference between ~~However, if~~ distinct therapeutic 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.	
216	17	Comment: "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." This sentence refers to the extrapolation of indications and breaks up the argumentation of the whole paragraph. It should therefore be discussed in section 6 Extrapolation of indications, if at all. The PK profiles in different therapeutic areas may be different solely on the basis of an altered antigen expression. However, this does not automatically implicate that the PK of the biosimilar would behave differently than the reference product in the different indications. Proposed change:	Not accepted. The choice of the indication for the PK study is one of the aspects that needs to be addressed in the PK section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Remove the sentence from this paragraph and discuss the possibility to support extrapolation of indications with separate PK studies in the corresponding chapter 6, if at all.	
216-218	5	Comment: The draft guideline states that if distinct therapeutic areas are involved for a particular mAb, separate PK studies may be recommendable as support for extrapolation between indications. In our view, extrapolation of pharmacokinetic findings should not be linked to whether the therapeutic areas or indications are distinct. Instead, the relevant question is whether the patients are different with respect to concomitant medication, comorbidities, or other factors that might influence PK, such as immunosuppression. For example, concomitant administration of methotrexate can influence the half-life of therapeutic antibodies to varying degrees. As a result, antibody differences between the reference product and the biosimilar may be masked or revealed by the concomitant use of	Not accepted. The burden of the justification of extrapolation is on the Applicant on a case by case basis. If PK comparability is convincingly shown in the most sensitive population from a PK point of view, it is not expected that an additional PK study in a less sensitive population would provide any useful information.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		methotrexate. Methotrexate use is common in rheumatoid arthritis, but less common is some other arthritides. Thus, rather than focusing on whether the therapeutic areas are distinct, the guideline should focus on whether concomitant medications and comorbidities or other relevant factors differ. Proposed change (if any): "~~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.~~ **However, if there are differences between indications in terms of concomitant therapies, comorbidities, or other relevant patient status factors (e.g., immunosuppression), separate PK studies will ordinarily be necessary to support extrapolation of clinical data from one to the other.**"	
216-218	7	Comment: The statement appears inconsistent with the principles expressed in lines 209-213 of the draft guideline. Autoimmune populations are often expected to be more homogenous and less variable than oncology populations, given the target expression, and therefore target-mediated PK effects are less variable and background medications can be more easily standardized. To illustrate this concept, the most prevalent antibody used in autoimmune and oncology	Not accepted. "Separate PK studies" is a general term that does not infer the type of methodology to be used; this would also cover population PK evaluation if adequately justified. In addition, population PK is mentioned later.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		indications is rituximab, which binds to CD-20 on B cells. The level of this target in autoimmune populations, while variable, is less variable than would be seen in an oncology population. Furthermore, comparative PK in the oncology population can be assessed by population PK assessments in therapeutic trials. As these trials are larger and more clinically realistic than separate PK studies, this may be a more sensitive way of assessing relative PK of the reference and biosimilar products. Proposed change: "However, if distinct therapeutic areas are involved for one particular mAb (e.g. autoimmunity and oncology), separate PK studies **or including population PK assessments in therapeutic trials** may be recommendable as a support for extrapolation between these indications."	
216-218	11	Comment: "separate PK studies may be recommended as a support for extrapolation". Should this not depend on the fact that the originator showed differences in PK by indication? For instance, if the MOA and the PK profile are similar across different therapeutic indications, extrapolation without separate PK studies might be very reasonable. The guidance should allow case-by-case justification.	Not accepted. The burden of the justification of extrapolation is on the Applicant on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "separate PK studies (especially, when there is evidence that MOA or PK profile may differ across indications) may be recommended as a support for extrapolation."	
216-218	15	Comment: The proposed text appears inconsistent with the concepts voiced in Lines 209-213 of the draft guideline. (See above.) Autoimmune populations are often expected to be more homogenous and less variable than oncology populations, given that target expression, and therefore target-mediated PK effects, are less variable and background medications can be more easily standardized. To illustrate this concept, the most prevalent antibody used in autoimmune and oncology indications is rituximab, which binds to CD-20 on B cells. The level of this target in autoimmune populations, while variable, is less variable than would be seen in an oncology population, and for this reason studying comparative PK in the autoimmune population would be consistent with the guidance provided in Lines 211-213, which states that more homogenous, sensitive populations be should be utilized for comparing product-inherent PK properties. Further, comparative PK in the oncology population can be assessed by population PK assessments in therapeutic trials. As these trials are larger and more clinically realistic than separate PK studies, this may be a more sensitive way of assessing relative PK of the	Not accepted. "Separate PK studies" is a general term that does not infer the type of methodology to be used; this would also cover population PK evaluation if adequately justified. In addition, population PK is mentioned later.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reference and test products. Proposed change: "However, if distinct therapeutic areas are involved for one particular mAb (e.g. autoimmunity and oncology), separate PK studies ***or including population PK assessments in therapeutic trials*** may be recommendable as a support for extrapolation between these indications."	
225 372 424	21	**Comment:** As an example: For HER2-positive patients, patients are not retested after initial diagnosis. It is not known what the effect of Herceptin treatment has on the tumour biology. Since the biosimilar is likely to not have exactly the same profile of the functional domains, it cannot be assumed that demonstration of efficacy in early breast cancer provides assurance of efficacy in later lines. **Proposed change (if any):** Please reconsider the approach	Please see chapter on extrapolation of indications.
225-227	22	**Comment:** For nonlinear drugs the statement "a comparison with the highest dosage regimen would be advisable" can be contradictory to the aim for the study design to be the most sensitive for differences because the highest dosage regimen may not be the regimen most sensitive to differences between reference and	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biosimilar products. It is more appropriate to have a qualifier such as "provided that the sensitivity to detect differences is similar across the range of dosage regimen." **Proposed Change:** We ask that EMA consider the alternative text that appears in line 291-292, "**Subject to reasonable justification, there is no need to test all therapeutic dosage regimens**."	
225-227	20	Comment: For nonlinear drugs the statement "*a comparison with the highest dosage regimen would be advisable*" can be contradictory to the aim for the study design to be the most sensitive for differences because the highest dosage regimen may not be the regimen most sensitive to differences between reference and biosimilar products. Unless the sensitivity to detect differences is similar across the range of dosage regimen the doses recommended in the label should be investigated. Proposed change: "In case of nonlinear PK with over proportional increase, ~~a comparison in the population with the highest dosage regimen would be advisable.~~ all dosage regimens in the label should be tested unless otherwise justified or unless a bracketing approach can address some dosage regimens."	Partially accepted. The revised version addresses the choice of the dose in more details.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
226-227	7	Comment: For nonlinear PK the statement "a comparison in the population with the highest dosage regimen would be advisable" appears to be contradictory to the aim of the study design to be the most sensitive for differences because the highest dosage regimen may not be the regimen most sensitive to differences between reference and biosimilar products. Proposed change: "In case of nonlinear PK with overproportional increase, a comparison in the population with the highest dosage regimen would be advisable**, provided that the sensitivity to detect differences is similar across the range of dosage regimens. Subject to reasonable justification, there is no need to test all therapeutic dosage regimens.**"	Partially accepted. The revised version addresses the choice of the dose in more details.
226-227	11	Comment: We request the following clarification: for compounds with greater than proportional increases in exposure with dose, is demonstration of similarity at the highest dosage regimen sufficient for establishing clinical biosimilarity, or should similarity also be established at another, lower dosage regimen? Agency guidance is requested on conditions in which testing a single higher dose will be sufficient, versus cases in which testing at multiple dose levels will be necessary.	Accepted. The revised version addresses the choice of the dose in more details. Ultimately, the Applicant has to justify the selection of the dose(s) on a case by case basis based on the data available for the reference product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
226-227	16	Comment: The current draft guideline does not provide a recommendation for cases of non-linear PK with less-than-proportional increase. Proposed change (if any): For those products with a non-linear PK with a less than proportional increase, it would be recommended to demonstrate pharmacokinetic comparability at the lowest clinical dose.	Partially accepted. The revised version addresses the choice of the dose in more details.
228	17	Comment: It may be necessary to perform the PK study in a different patient population than the clinical trial designed to establish similar clinical efficacy …" PK studies can also be done in healthy volunteers, therefore remove the word patient. Proposed change: It may be necessary to perform the PK study in a different ~~patient~~ population than the clinical trial designed to establish similar clinical efficacy,…….	Accepted.
228-231	17	Comment: „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	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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." Since comparative PK study is also done in patients for many mAbs where efficacy data is also collected, using the term „pivotal" or „clinical efficacy trial" to show biosimilarity instead of „phase III" would be more appropriate. Proposed change: „In such scenarios, population PK measurements of sampling during the ~~phase III study~~ **clinical efficacy trial** are recommended as additional information…"	
228-231	20	Comment: To perform a PK study in a different population than the clinical trial to establish efficacy seems problematic because dose-response-relationship cannot be investigated, in other words the PK profile established in one population may not be relevant for the efficacy and safety profile explored in a different population leading to uncertainty and potential misinterpretation of findings. Not sure if pop PK measurements can sufficiently address this concern.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design and the possibility to extrapolate on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We suggest that the guidance more clearly defines typical criteria or conditions which would justify (single dose) PK study in a different population allowing for extrapolation to a different (target) population.	
228-233	11	Comment: Different populations may be needed for clinical PK and equivalence testing. This recognizes that homogeneity affects clinical efficacy and PK differently, which is correct. The additional collection of PK should not be mandated, or a condition of approval when it is recognized that the population used for clinical equivalence may well have more variability and less uniform data collection that the specially designed PK study. We agree with the agency recommendation to collect pop-PK samples in clinical efficacy studies. Clarification requested: would it be acceptable to collect pop-PK samples and characterize PK in only a subset of the clinical efficacy study population? Collecting pop-PK samples at all clinical sites is not always feasible due to logistical concerns (e.g. not all sites have the ability to properly collect, process and store PK samples). Proposed change (if any): Establishing PK bioequivalence in all indications for a biosimilar may not be required if originator has similar	Not accepted. The onus is on the Applicant to justify if there is a need for additional PK data and what type of data can be used on a case by case basis. The guideline cannot envisage all possible situations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		PK across indications, and PK bioequivalence has been demonstrated for a biosimilar in animals and in a sensitive population. In case it is required to establish PK bioequivalence in different indications, it may be acceptable to collect PK samples and characterize PK in only a subset of the indicated populations.	
228-233	17	Comment: „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." It is known from the literature that for some mAbs the PK is similar across indications or in some cases has not been addressed for all indications of the reference mAb. Therefore in such cases PK assessment should not necessarily be needed in multiple indications even in cases when PK is assessed in one indication and similar clinical efficacy is assessed in another indication. Please supplement the guidance accordingly.	Not accepted. The onus is on the Applicant to justify if there is a need for additional PK data and what type of data can be used on a case by case basis. The guideline cannot envisage all possible situations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
229-230	21	**Comment:** "PK measured most sensitively": what does this mean? **Proposed change (if any):** Please clarify	
229-231	10	Comment: The sentence "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" implies that PK comparability studies may be done in populations different from the desired indications population by the biosimilar manufacturer. Proposed change (if any): This should be strengthened by additional statement that, in such circumstances, strong rationale and data should be provided to support the notion that PK comparability is expected between the two different populations, and this might have to include PK data from two separate populations that are different from the desired indications population, to demonstrate that PK comparability already exists across different populations. Careful consideration should be taken to account for the differences both innate and external to the populations being considered and compared to, such as classic clinical pharmacology demographics	Not accepted. This is not what is stated in the guideline. The most sensitive population for PK comparability may be different from the most sensitive population for efficacy comparability. This is not related to the indications claimed by the biosimilar manufacturer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		parameters (age, gender, renal, hepatic, etc.), as well as the different type of drug-drug interactions that might occur in the respective populations.	
231	12	Comment: The word "sensitively" typically means sympathetically, delicately, understandingly; in my opinion these synonyms do not fit the message. Proposed change (if any): Do you mean "most objectively" or with the "highest degree of sensitivity" or "accurately"?	Accepted. The sentence has been changed.
231-233	21	**Comment:** reference to "the phase III study" is ambiguous. Is this implying the original phase III study for the reference product? If so, how can the originator company be expected to measure data which might be required by a biosimilar company at some time in the future? If it means the phase III study for the biosimilar, then it is not clear if biosimilars need "phase III" studies in the sense we usually think of them. Generally, the reader would benefit if the guideline would clarify what is meant with phase I, phase II and phase III studies in the context of biosimilar mAbs.	Accepted. The sentence has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Possible change in the text could be: "… sampling during the head-to-head equivalence study…" [if that is the meaning implied]	
233	20	Comment: We agree with the concept that once biosimilarity has been established between biosimilar and innovator, the established properties of the innovator molecule (e.g. behaviour in special populations, metabolic profile, etc.) can reasonably be considered to apply to the biosimilar molecule, when scientifically justifiable. Proposed change: We request that the agency add a sentence specifically addressing DDI studies to section 5.1.2. For example, "Drug-drug interactions studies are not normally required as the overall objective of the development program is to establish biosimilarity. Once biosimilarity is established, the known DDI profile of the innovator compound can reasonably be considered to apply to the biosimilar molecule."	Not accepted. It is not considered necessary to list in the guideline all the studies that are not required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
234	21	**Comment:** It would be helpful to clarify with examples in what case is a multidose PK study required **Proposed change (if any):** See comments to lines 201-203, 214-215, 235-242	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis. This cannot be covered within this general guideline.
234-242	22	**Comment:** We ask that EMA clarify the conditional requirements for multidose PK and indicate that class-by-class discussions could be available to sponsors.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis. This cannot be covered within this general guideline.
234-279	17	Comment: In the relevant biosimilar guide (EMEA/CHMP/BMWP/42832/2005) it is stated that „The choice of the design for single dose studies, steady-state studies, or repeated determination of PK parameters should be justified by the applicant." In this chapter the choice of single dose PK and repeated determination of PK parameters should be further elaborated. It is also stated that „If a multidose PK study in patients is performed, sampling should normally be undertaken after the first dose and later, preferably at steady state." However it may also be the case that the	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis. As highlighted in the comment, not all situations can be covered within this general guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		therapeutic regimen ends before the steady state PK could be reached and for such cases some additional guidance would be helpful and is kindly requested.	
234-279	20	Comment: Please see previous comments on lines 201-207: "Clearance and other pharmacokinetic parameters may change after first dose due to immunogenicity, disease progression etc., hence a single dose evaluation will not correctly describe the true profile in the context of safety/tolerability and therapeutic response of a biosimilar." Proposed change: Please see comments to lines 201-207.	Not accepted. The onus is on the Applicant to justify the most appropriate PK design on a case by case basis. This cannot be covered within this general guideline.
236-238	20	Comment: For long acting, long half life biologicals, it is difficult to reconcile the need for Cmax, especially if there has not been a demonstration of a safety issue with the innovator related to Cmax. We suggest that in general, AUC be typically considered of greatest importance, followed by Cmax, and then Ctrough, though the choice of parameters may depend on indication, dosage formulation and other factors. For biologics, we contend that Ctrough may under certain circumstances	Accepted. The revised version details the recommended PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be less important due to subject-to-subject differences in immunogenicity and receptor mediated clearance. The importance of Cmax may depend on the therapeutic application of the molecule in question. We recommend addition of language addressing the above points to the guidance. Proposed change: The single best parameter, from among AUC, Cmax, Ctrough should be identified and justified as the primary endpoint for comparative PK studies.	
237	16	Comment: The current draft guideline mentions that the PK endpoints would depend on the type of mAbs and PK characteristics (linear or non linear). This implies that the PK endpoints in case of linear PK would be different from the PK endpoints in case of non-linear PK. However, the preferred endpoints for these different situations, linear versus non-linear and/or different types of mAbs, are not reported. Proposed change (if any): The current draft guideline could give more clarification on how different mAbs and different PK profiles may influence the choice of the endpoints .	Accepted. The revised version details the recommended PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
237-238	11	Comment: We request additional clarification as to which of the three parameters mentioned (AUC, Cmax and Ctrough) are primary parameters that should be met within BE bounds. We suggest that in general, AUC be typically considered of greatest importance, followed by Cmax, and then Ctrough, though the choice of parameters may depend on indication, dosage formulation and other factors. For mAbs with a long half life, it is difficult to reconcile the need for Cmax, especially if there has not been a demonstration of a safety issue with the innovator related to Cmax. For these biologics, we contend that Ctrough may under certain circumstances be less important due to subject-to-subject differences in immunogenicity and receptor mediated clearance. We recommend addition of language addressing the above points to the guidance. Proposed change (if any): "AUC should be the primary endpoint for comparison in BE studies. Other parameters may be included based on scientific justifications."	Accepted. The revised version details the recommended PK endpoints.
238-239	7	Comment: Determination of the "other PK parameters like clearance and half-life" is often not feasible for multidose studies because the chosen dosing interval may not allow adequate PK sampling. Additionally, target-mediated drug disposition is commonly observed	Accepted. The revised version details the recommended PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for mAbs. In those situations, it is not relevant to estimate clearance and half-life.	
239	22	**Comment:** Determination of the listed other PK parameters (*i.e.,* CL and t1/2) is often not feasible for multi-dose studies because the chosen dosing interval may not allow adequate PK sampling. Additionally target-mediated drug disposition is commonly observed for mAbs. In those situations, it is not relevant to estimate CL and t1/2. **Proposed Change:** It is recommended that the sentence starting with "Other PK parameters like clearance and half-life…" should be deleted from the text..	Accepted. The revised version details the recommended PK endpoints.
239	20	Comment: Determination of the listed other PK parameters (i.e. CL and t1/2) is often not feasible for multi-dose studies because the chosen dosing interval may not allow adequate PK sampling. Additionally target-mediated drug disposition is commonly observed for mAbs. In those situations, it is not relevant to estimate CL and t1/2.	Accepted. The revised version details the recommended PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The determination of CL and t1/2 should be conducted on a case by case basis.	
239-242	5	Comment: In discussing multidose PK studies, the draft guideline states that if relevant differences occur in PK parameters, the assumption of similar PK might be seriously questioned. We would strengthen this point. If there are "relevant" differences in PK, the assumption of similar PK is no longer valid. Proposed change (if any): "If relevant differences occur the assumption of similar PK **will be rejected**~~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."	Accepted. The wording has been changed.
239-242	20	Comment: "*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.*" If the differences are indeed relevant, that would imply that they affect clinical outcomes, and in this case the products are not biosimilar.	Accepted. The wording has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The statement should read "If relevant differences occur the assumption of similar PK would not be demonstrated."	
244	7	Comment: Clarification is requested on the term "long loading dose interval".	Accepted. 'Loading' has been deleted.
244	22	**Comment:** The phrase "long loading dose interval" is not a conventional term. **Proposed Change:** We ask EMA to please clarify what is meant by "long loading dose interval."	Accepted. 'Loading' has been deleted.
250	1	Comment: ADA measurements in parallel with AUCSS, CmaxSS, CtroughSS is typically not feasible especially at Cmax due to drug interference in ADA assays. Proposed change (if any): Please rephrase: "The ADAs should be measured in parallel if drug tolerance of the assays permits it."	Partially accepted. ADAs should always be measured but the timing of ADA measurement should depend on the specific assays used and the degree of drug interference. The wording has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
250	17	Comment: The analysis of anti-drug antibodies at Cmax steady state is typically not feasible due to drug interference in the ADA assay. Proposed change: Please rephrase: **"**Thus, anti-drug antibodies should be measured in parallel **given that the assay format has a suitable drug tolerance. Otherwise, appropriate sampling time-points need to be chosen".**	Partially accepted. The wording has been changed.
251-259	20	Comment: The criteria to demonstrate equivalence is an important topic and should be addressed as a separate section, as they apply to both single and multi-dose PK studies.	Accepted. The revised version is more detailed.
251-279	21	**Comment:** All of this is relevant to single dose as well as multiple dose studies. **Proposed change (if any):** Either change heading for section 5.1.3 or introduce a new section.	Accepted.
251 – 279	3	Comment: All of this is relevant to single dose as well as multiple dose studies.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Either change heading for section 5.1.3 or introduce a new section.	
253-255	10	Comment: The statement regarding cases where PK comparability is proposed to be established beyond the usual 80-125% threshold needs to be strengthened. Proposed change (if any): Statement such as, "in these situations whereupon the usual 80-125% threshold is not to be used for determining PK comparability between products, additional clinical trials demonstrating comparable safety, tolerability, and efficacy will generally be required."	Not accepted. There is currently a lack of experience on the value of these margins and thus, a flexible approach is considered more appropriate.
253-255	17	Comment: The standard equivalence margins of 80-125% are defined for bioequivalence studies of chemical entities, ideally explored in cross-over designs. The widening of the acceptance range for highly variable drug products is justified by a replicate cross-over design. However, there is no algorithm established for biosimilars and the parallel design. An estimation of variability can only be based on published data of the reference product. For highly variable mAbs it has to be assumed that even two different batches of the comparator would not match the standard equivalence criteria in a parallel	Partially accepted. Part of the addition proposed does not provide any further advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		design study. Proposed change: Add after "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". **"Highly variable mAbs, for which a wider difference of the parameters of interest is considered clinically irrelevant, can be assessed with a widened acceptance range. The extent of the widening should be based upon the variability seen for the reference treatment in the PK equivalence study. The request for widened acceptance range should be discussed with the authority and prospectively specified in the protocol."**	
257	11	Comment: The language "a significant difference, yet fulfilling equivalence criteria" is confusing and needs clarification on how to determine what a significant difference is. It would also be helpful if some examples are provided.	Accepted. This sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
257-259	21	**Comment:** "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." To us it would be a sign that the set equivalence margins were not appropriate. In addition, the word "significant" is ambiguous between clinical and statistical. "Statistically significant" is intended? **Proposed change (if any):** The wording is unclear and needs to be revised. In addition, the general predetermined margins in the current text might need justification?	Accepted. This sentence has been deleted.
257-259	22	**Comment:** The sentence "A significant difference, yet fulfilling equivalence criteria…" should be clarified to explain what types of statistical evaluation could result in a conclusion of significant difference within the context of an equivalence evaluation. A separate test for significance is not typically performed within an equivalence evaluation, and could undermine the integrity of the pre-defined equivalence acceptance criteria.	Accepted. This sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The wording is unclear and needs to be revised.	
257-259	3	Comment: This statement will potentially punish a study with a larger sample size (as it will have a narrower confidence interval, which in turn is more likely to exclude 1 and therefore indicate a statistically significant difference between both treatments). If a treatment fulfils the bioequivalence criterion, then it should not matter if there is a statistically significant difference between both treatments. Proposed change (if any): Delete sentence.	Accepted. This sentence has been deleted.
257-259	17	Comment: If the PK assessment is performed as part of the clinical study designed to establish similar efficacy and safety (e.g. for mAbs where PK is highly variable even within one clinical indication), a significant difference may likely occur due to a high sample size, even though bioequivalence has been proven. This will not question the biosimilarity concept per se. Proposed change: Delete the sentence: ~~A significant difference, yet fulfilling equivalence~~	Accepted. This sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~criteria, may indicate differences in the interaction between the target antigen(s) and the biosimilar mAb, and thus may question the biosimilarity concept.~~	
258	21	**Comment:** ...interaction between the target antigen(s) and the biosimilar mAb... should include mention of altered interaction with non-specific targets and the biosimilar. **Proposed change (if any):** "...interaction between specific and/or nonspecific target antigen(s) and the biosimilar mAb..."	This sentence has been deleted.
258	20	Comment: *"...interaction between the target antigen(s) and the biosimilar mAb..."* should include mention of altered interaction with non-specific targets and the biosimilar. Proposed change: "...interaction between ~~the~~ specific and/or nonspecific target antigen(s) and the biosimilar mAb..."	This sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
259-259	20	Comment: "The sentence "*A significant difference, yet fulfilling equivalence criteria […]*" should be clarified to explain what types of differences are being referred. This could be supported by some examples, if any. An equivalence test cannot be construed as a test for differences, so the sentence construction would appear to suggest a separate, post-hoc significance test for differences. Such is not normally required in bioequivalence testing and would appear to undermine the integrity and credibility of the pre-defined acceptance criteria. Proposed change: The wording needs to be revised.	Accepted. This sentence has been deleted.
260	21	**Comment:** "...should precede clinical trials." **Proposed change (if any):** "...should precede clinical efficacy trials."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
260	7	Comment: We suggest revising the statement. Proposed change: "~~Usually p~~ **P**roof of ~~similar~~ **equivalent** PK profiles should precede **Phase III** clinical trials.	Not accepted. There are cases as explained in the guideline where PK comparison may be part of the comparative efficacy trial.
260	17	Comment: What is the scientific reason for requesting human PK data to be available prior to start Phase III clinical trials? If quality and non-clinical data support biosimilarity of test and reference product, there is no risk for the patient when starting Phase I and III simultaneously. This is further supported if animal PK data is available. Due to the long time lines for performing Phase III trials, requesting per se a sequential start would further delay market access of the biosimilar product. Even if PK data did not meet equivalence margins due to high variability, similar efficacy and safety could still be established by Phase III trials, thus combined with quality and nonclinical data, form the basis for biosimilarity assessment. Therefore, we recommend deleting this sentence Proposed change: ~~Usually, proof of similar PK profiles should precede clinical trials~~	Not accepted. The standard biosimilar approach is stepwise. The comparative efficacy trial should only be started after PK comparability has been shown. Relevant PK differences would be expected to preclude starting the efficacy trial especially when a suboptimal treatment would negatively impair the patient prognosis. The efficacy model is usually not the most sensitive to detect differences between the biosimilar and reference product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: It is not clear if phase III trials are meant by **"**clinical trials**"**. Proposed change: Please be more specific.	Accepted.
260	20	Comment: *"...should precede clinical trials."* Proposed change: "...should precede clinical efficacy trials." Comment: A normal cohort dose-escalation study should be performed for the biosimilar, unless there is adequate support for starting initial PK studies at the labelled dose and the exploratory PK comparison with the reference can be made when reaching the upper-middle therapeutic dose range if multiple cohorts are required. This is especially important for a reference mAb with known steep DR relationship and/or nonlinear PK.	Accepted. A normal cohort dose-escalation study is usually not expected in a biosimilar development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
260-267	20	Comment: "*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.*" It is not understood in which circumstances, and why such highly abridged development (neither non-clinical nor phase 1) would be appropriate, without compromising safety, and be regarded as ethical. Appropriate, stepwise, comparative quality, non-clinical, human PK/PD, and safety and efficacy studies in relevant indications are needed on all biosimilars. Proposed change: Please clarify, and remove options for questionable alternatives from the guidance. Please remove Phase I as this is misleading in the context of biosimilar. We recommend that comparative PK studies generally precede clinical efficacy trials unless such studies can be credibly conducted as the initial stage of clinical efficacy trials in a sufficient number of patients to fully characterise the PK. An interim analysis of the data should occur as soon as practically possible to ensure patient safety.	Partly accepted. "Phase I" has been removed. The other comments do not seem to provide more information than the current guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
260-270	20	Comment: Lines 260-264 correctly acknowledge that PK can often be highly variable within a single indication and that, in such a case, PK may need to be explored as part of a clinical efficacy trial. The CHMP should add, however, that some differences in PK characteristics will still not be apparent in a clinical trial as trials may have relatively homogeneous patient populations. Therefore, applicants may need to conduct additional PK tests in specific subpopulations. Proposed change: In the middle of line 270, the CHMP should insert the following sentence: "On a case-by-case basis, the Applicant may need to supplement this clinical efficacy trial with additional PK studies or population PK assessments in patient subpopulations."	Not accepted. The potential need for additional PK is already mentioned in the guideline on a case by case basis.
260 - 271	5	Comment: On line 261, the draft guideline notes that PK can often be highly variable within a single indication. We agree that in these cases, differences in PK may become evident only in a larger clinical study and that PK comparisons should also be explored in those larger efficacy studies. The guideline should also note that because some differences may be apparent only in subpopulations (e.g., those based on age, immune status, or concomitant medications), this work may need to be supplemented with subpopulation specific PK	Not accepted. The guideline already recommends the choice of the most sensitive population to demonstrate PK equivalence and this has to be justified by the Applicant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		analyses. Proposed change (if any): The CHMP should amend the draft guideline to recognize that in some situations, biosimilar applicants should also study the PK of a proposed biosimilar in patient subpopulations.	
260-279	22	**Comment:** The section on non-determinative PK studies (where variable response is expected) is general in nature and should be in the general guideline.	Partly accepted. Although this is true, the issue was not raised for previously considered biosimilars.
260-279	22	**Comment:** We suggest EMA include consideration of an exploratory PK study as part of an investigation of tolerability and initial trend for evidence of PK equivalence. Formal PK can be assessed as part of efficacy assessment in a larger study. **Proposed change:** We suggest line 260 be revised as follows: "Usually, proof of similar PK profiles should precede **confirmatory** clinical trials."	Accepted. The sentence has been changed to "clinical efficacy trials".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
261-270	17	Comment: In case of expected high variability of PK in patients, an exploratory first part to obtain preliminary PK data is of no value as this is not a guarantee that more stringent PK equivalence parameter will be met in the confirmatory part of the study. We think that the decision on whether it is appropriate to start a comparative clinical efficacy study in parallel with a PK study or having the PK assessment as part of the Phase III trial, should be decided on a case by case basis depending on the data (quality, non-clinical) and observed differences in profile. The whole concept of biosimilarity is based on building up confidence from stringent and comprehensive quality testing, via in-vitro and, if appropriate, in-vivo studies. Proposed change: To reword the paragraph from line 260 to 270.	Accepted. A sentence has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
267	21	**Comment:** "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." It is not understood in which circumstances, and why such highly abridged development would be appropriate, without compromising safety, and regarded as ethical. Appropriate, stepwise, comparative quality, non-clinical, human PK/PD, and safety and efficacy studies in relevant indications are needed on all biosimilars. **Proposed change (if any):** "..Please clearly, and remove options for questionable alternatives from the guidance. Please remove Phase I as this is misleading in the context of biosimilar. We recommend that comparative PK studies are a prerequisite to clinical efficacy trial.	Partly accepted. "Phase I" has been removed. An additional statement has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
267-270	11	Comment: The Draft Guidance states that it "could become problematic", "to start with a comparative clinical efficacy trial that includes PK, without formal phase I study, … with potentially limited non-clinical data …" But it is not clear whether this would be allowed, though problematic, in certain situations. If so, the guidance should specify such situations.	Partially accepted. A further general statement has been added.
267-271	3	Comment: As indicated in Section 5.1.2, PK studies are most likely to be performed in patients. Therefore conducting a clinical efficacy trial which also collects PK data should not be regarded as any different to conducting a PK trial as both trials would use the same patient population. Sentence in Lines 270-271 seems to imply the combination of data from of an "early," small exploratory study with that of a later more extensive study (in a sort of "seamless phase I-III" type of design), but it is not clear. Proposed change (if any): Reword sentence to "If it is not possible to conduct a Phase I PK study in healthy volunteers, then it would be acceptable to combine clinical efficacy data from PK/PD studies with data from a clinical efficacy study. In that	Not accepted. The approach taken to collect exploratory PK data is the Applicant's choice and various options are possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		case proper measures have to be pre-planned to ensure the statistical rigour and integrity of this trial".	
270-271	21	**Comment:** This sentence might be implying the combination of data from of an "early," small exploratory study with that of a later more extensive study (in a sort of "seamless phase II-III" type of design) but the approach is not clear. **Proposed change (if any):** "If clinical efficacy data from PK/PD studies are to be combined with data from a clinical efficacy study, then proper measures have to be pre-planned…"	Not accepted. The approach taken to collect exploratory PK data is the Applicant's choice and various options are possible.
273	21	**Comment:** reference to "the interim analysis". No interim analysis has previously been mentioned? Clarify. **Proposed change (if any):** Suggest deletion of this part of the sentence so it reads "It may be necessary to consider access to unblinded PK data, which usually need not include..	Accepted. This has been clarified.
273	3	Comment:	Accepted. This has been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Reference to "the interim analysis". No interim analysis has previously been mentioned Proposed change (if any): Suggest delete this part of the sentence so it reads "It may be necessary to consider access to unblinded PK data, which usually need not include…" Proposed change (if any): Suggest delete this part of the sentence so it reads "It may be necessary to consider access to unblinded PK data, which usually need not include…"	
273-277	20	Comment: To clarify wording, the following updated text is proposed. Proposed change: **"**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). This may result in design modifications or additional interim analyses. Access to unblinded PK data needs to be controlled and 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."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
280	20	Comment: The title of section 5.1.4 "*5.1.4. Additional considerations for PK measurements of cytotoxic mAbs in anticancer indications*" should be broadened since the mechanism of action of anticancer therapies may not always be directly cytotoxic. Proposed change: 5.1.4. Additional considerations for PK measurements of ~~cytotoxic~~ mAbs in anticancer indications	Accepted.
280-281	22	**Comment:** While the title of 5.1.4 refers to "cytotoxic mAbs in anti-cancer indication," the essence of the described situation actually applies to all mAbs that have PD mediated drug disposition. **Proposed change:** We suggest EMA broaden the scope by either changing the title or including a statement in this section to state that the described cases for anticancer cytotoxic mAbs can apply to other indications where PK induces PD change, which in turn affects the PK disposition.	Accepted.
280-299	7	Comment: Section 5.1.4 could be relevant to any indication/therapeutic area where drug effect and PK are inter-related, i.e. PK is affected by PD. It should cover other mechanisms of action of anti-cancer	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products than cytotoxics.	
283	21	**Comment: "**(in case of response increase of half-life with multiple dosing)." Parenthetical statement unclear. **Proposed change (if any):** Revise	Accepted.
283	7	Comment: Clarification is requested on the statement "in case of response increase of half-life with multiple dosing"	Accepted.
283	22	**Comment:** It is not clear what "in case of response increase of half-life" means. **Proposed change:** We ask EMA to please clarify what is meant by "in case of response increase of half-life."	Accepted.
290	3	Comment: Use of the word "comparability" may be ambiguous. Proposed change (if any): Suggest use the word "equivalence"	Not accepted. "Comparable" rather than "equivalent" is a preferred term for biosimilars.

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290-291	21	**Comment:** "….should be designed to demonstrate clinical comparability selecting the most sensitive PK parameters" The PK parameters are usually predefined. It is not clear how to select the most sensitive key PK parameters prior to conducting a comparative PK study. When population PK approach is used to compare PK, will compartmental PK parameters (e.g., CL, V) be compared? In case PK/PD/efficacy/safety correlations have been established for the reference mAb where specific PK parameters drive the outcome, similarity for the most relevant PK parameters should be studied. Therefore, justification of the PK parameter needs to be provided in the clinical context. **Proposed change (if any):** Need further clarity on "sensitive PK parameter" Suggest changing sentence to "….should be designed to demonstrate clinical similarity selecting the most sensitive PK parameters in the clinical context"	Accepted. The sentence has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
291-292	21	**Comment:** "Subject to reasonable justification, there is no need to test all therapeutic dose regimens" We feel that the wording "there is no need to test" is too strong. **Proposed change (if any):**	Accepted.
292-295	7	Comment: It should be emphasised that the combination with chemotherapy may need to be studied even if the monotherapy setting is preferred to minimize variability.	Not accepted. Extrapolation has to be justified by the Applicant on a case by case basis.
293-295	21	**Comment:** " It is usually recommended to study the comparative PK in the monotherapy setting in order to minimize sources of variability, although chemotherapy often does not significantly alter PK characteristics" We agree that chemotherapy does not alter mAb PK. However, we do not agree that a monotherapy setting is preferred as such, as it may not reflect the clinical use of the antibody. **Proposed change (if any):** PK similarity should be assessed in a clinically relevant setting (monotherapy or	Not accepted. The most sensitive model should be used to demonstrate PK comparability and justified by the Applicant. It may be a regimen that is not the most commonly used in clinical practice.

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		combination therapy) with appropriate justification for the choice proposed. It might be most appropriate to assess this in the therapy used in the reference product's efficacy trials.	
293-295	11	Comment: In cases in which both monotherapy and combination therapy are approved because concomitant chemotherapy increases efficacy, it may not be ethical to conduct a comparative PK study in a monotherapy setting. We suggest that the agency add a statement allowing flexibility for conduct of the comparative PK study in either a monotherapy setting or in a combination setting based on scientific justification and rationale.	Partly accepted. "If feasible" has been added.
296-299	7	Comment: We agree with this concept, which further supports our comments for lines 216-218 above. However, the guideline could also reflect that, for those antibodies with an appropriate safety profile, PK studies in healthy	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		volunteers (the most homogenous population available) should be mentioned as a possibility. Proposed change: "With regard to the "model" ~~indication~~ **population** for a comparative PK study, an adjuvant setting in patients with early cancer, if possible, may be advisable, since the tumour burden is low, **or a study in healthy volunteers may be considered if the safety profile of the reference product makes this acceptable**. However, clearance due to mAb-antigen interaction will not be captured, **and given this population PK in therapeutic studies may be required in such situations**. Thus, the choice of the population should be justified accordingly."	
296-299	15	Comment: We agree with this concept, and note that it further supports our comments on Lines 216-218 above. However, the text could also reflect that, for those antibodies with an appropriate safety profile, PK studies in healthy volunteers (the most homogenous population available) should be mentioned as a possibility. Proposed change: "With regard to the 'model' ***population*** for a comparative PK study, an adjuvant setting in patients with early cancer, if possible, may be advisable, since the tumour burden is low, ***or a study in healthy volunteers may be considered if the safety profile***	Partially accepted. The use of healthy volunteers has been addressed in section 5.1.1, Study design.

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		of the reference product makes this acceptable. However, clearance due to mAb-antigen interaction will not be captured, ***and given this population PK in therapeutic studies may be required in such situations***. Thus, the choice of the population should be justified accordingly."	
301	5	Comment: Draft guideline § 5.2 states that PK studies can be combined with PD endpoints, where available. It also notes that there is often a lack of specific PD endpoints and that the emphasis will often be on non-clinical (*in vitro*) PD evaluations. We generally agree with these points but recommend emphasis on comparing the PK/PD relationships of the products. Current PK assay methodologies are limited and thus may not reveal all relevant differences between the products. PD endpoints, even when not validated, may be sensitive to minor differences between the products. Proposed change (if any): ~~"Pharmacokinetic studies can be combined with pharmacodynamic (PD) endpoints, where available.~~ **Applicants should incorporate PK endpoints in the PD evaluations in order to**	BMWP agrees. This proposal has been put to final guideline draft.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		compare the PK/PD relationship of the reference product and the proposed biosimilar."	
301	17	Comment: It needs to be emphasized that comparative PD study alone together with sufficient safety data could be able to demonstrate comparability of the biosimilar and the reference products. It is supported by the facts that PD parameters show less variability while efficacy endpoints present more variability related to the diversity of the hosts which is ultimately unrelated to the drug activity. Consequently, well established PD endpoints supported by broad set of comparative *in vitro* assay studies carried out in the non-clinical program would be highly predictive and provide more sensitive tools to assess comparative efficacy.	Comment noted. However, BMWP considers that this scenario is well covered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
301	20	Comment: Clinical PK/PD studies may allow for the sensitivity to detect a difference between innovator and biosimilar but usually these studies alone are not sufficient to demonstrate biosimilarity for the following reasons: (1) many PD markers have low predictability for efficacy and safety; 2) no surrogate markers are available for the current approved mAbs in oncology and immunological conditions and 3) comparable immunogenicity and safety could not be adequately assessed in these trials due to size and duration.	Comment noted, but no change to text warranted apart from the proposals made in the updated draft.
301-303	21	**Comment:** Relying solely on *in vitro* testing to establish comparable PD in case of lack of specific PD endpoints appears problematic. As it stands, the relevance of this paragraph to the whole section is not entirely clear. Stand alone *in vitro* testing is probably not sufficient. **Proposed change (if any):** It would be important to clarify in the guideline in which context *in vitro* testing could supplement the investigation of dose-concentration-response-relationships.	BMWP considers that the current text proposal allows for flexibility while still be subject to a strong case-by-case scientific justification.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
301-303	20	Comment: The introduction to the PD section indicates that PD studies will often be non-clinical (line 302-303), but intro to efficacy section wants the PD to be in a 'clinically relevant manner' - does this rule out most non-clinical PD studies as adequate then? Relying solely on *in vitro* testing to establish comparable PD in case of lack of specific PD endpoints appears problematic. As it stands, the relevance of this paragraph to the whole section is not entirely clear. Stand alone *in vitro* testing is probably not sufficient. The criteria regarding PD studies which would then trigger the requirement for clinical studies need to be clarified. Proposed change: It would be important to clarify in the guideline in which context *in vitro* testing could supplement the investigation of dose-concentration-response-relationships.	Partly agreed. Thetext has been made clearer.
302-303	22	**Comment:** The text suggests that *in vitro* testing could somehow compensate for the lack of PD endpoints that could be studied clinically. Further, it refers to *in vitro* pharmacology tests as non-clinical PD evaluations. *In vitro* pharmacology tests can certainly provide some insight into the comparative functionality of a biosimilar, but cannot be expected to reconstitute or predict *in vivo* pharmacodynamics. Thus, the emphasis of this text should be that the relevance of *in vitro* pharmacology studies to predict *in vivo*	Not accepted. BMWP considers that this is a too strong wording, given also that in the further course of the guideline text there is cross-reference from the safety section to this part.

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		pharmacodynamics will be limited, and that comparative efficacy studies will be required in these situations. **Proposed change:** We suggest the alternative text, "**In these situations in vitro non-clinical pharmacology studies cannot be expected to predict the similarity of the pharmacodynamics in vivo, and comparative efficacy studies will be required.**"	
304	17	Comment: Regarding the dose-concentration-response relationships, the burden of investigating or confirming these relationships should not be borne by the biosimilar applicant. Biosimilarity should be based on comparing other quality, non-clinical, and clinical characteristics. Additionally, it may be unethical to explore dose-concentration responses in oncology settings. If investigation of such relationships is deemed ethical, it should only be applied in situations where the resulting data can be used to reduce the burden of a Phase III study. Proposed change: It is recommended to delete the requirement to study the dose-concentration-response relationship from the	The wording in the draft guideline text has maybe been misunderstood, since the exploration of dose-response relationships is a recommendation for a possibility to support the biosimilarity exercise in a potentially powerful way ("should always explore"), not a requirement for generation of data. The investigation of dose-response relationships is not done for gaining more knowledge on the compound per se, it is done to generate a potentially powerful dataset. BMWP agrees that in many instances the testing of a lower (or too low) dose may be problematic, but this is covered already (lines 309-311 of the draft guideline). Nevertheless, this possibility should be mentioned.

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		guidance document as a critical measure of biosimilarity. If evaluation of this relationship is required, it may be best studied in a non-clinical setting.	
305-312	7	Comment: See comments for lines 60-62 above. Proposed change: "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. **However, it is recognized that use of the antibody at near saturation levels may be the only feasible clinical trial scenario if the reference product has only been approved and shown to have efficacy at doses close to the saturation point.** It is **also** 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. **In addition, where no sensitive PD marker is available, comparative testing of a range of doses may be statistically and/or practically unfeasible. Finally, in some cases testing a range of doses may not be**	Reasoning accepted. The text has been revised (not all proposals taken, since some are already implicitly included).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ethically or clinically feasible. However, for some reference mAbs clinical conditions may exist where such studies are feasible."	
305-312	15	Comment: We have previously addressed this general concept in reference to Lines 60-62 above. To reiterate, this approach is valid for those biologics, such as cytokines, that are approved for use at multiple or variable doses, when these doses lie on a reasonably steep portion of the dose-response curve, and for which a sensitive pharmacodynamic (PD) marker is available. We note, however, that most approved antibodies are highly targeted therapies that are generally used and approved at or near the top of their dose-response curve; many also do not have sensitive PD markers. We believe it would be inappropriate (and often clinically infeasible) to study reference product antibodies at doses other than those that are approved. Proposed change: "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. ***However, it is recognized that use of the antibody at near saturation levels may***	This is a repetitive comment. Please see comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be the only feasible clinical trial scenario if the reference product has only been approved and shown to have efficacy at doses close to the saturation point. It is ***also*** 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. ***In addition, where no sensitive PD marker is available, comparative testing of a range of doses may be statistically and/pr practically infeasible. Finally, in some cases testing a range of doses may not be ethically or clinically feasible.*** However, for some reference mAbs clinical conditions may exist where such studies are feasible."	
305-312	20	Comment: Most approved antibodies are highly targeted therapies that are generally used and approved at or near the top of their dose-response curve; many also do not have sensitive PD markers. We believe it would be inappropriate (and often clinically infeasible) to study reference product antibodies at doses other than those that are approved. Proposed change: "A single or repeat dose study in the saturation part of the dose-concentration-	This is a repetitive comment. Please see response above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. However, it is recognized that use of the antibody at near saturation levels may be the only feasible clinical trial scenario if the reference product has only been approved and shown to have efficacy at doses close to the saturation point. It is also 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. In addition, where no sensitive PD marker is available, comparative testing of a range of doses may be statistically and/or practically infeasible. Finally, in some cases testing a range of doses may not be ethically or clinically feasible. However, for some reference mAbs clinical conditions may exist where such studies are feasible."	
307-312 347-348	17	Comment: It is stated in chapter 5.2 on PD that „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	It is acknowledged that this appears to sound contradictory at first glance. However, BMWP had scenarios in mind where the safety of patients would not be compromised, e.g. for mAbs with very low immunogenicity in an anticancer "watch and wait" indication where a patient is normally not treated, but where a low dose of the mAb would notbe harmful (but rather may be beneficial). Such scenario is hypothetical, and therefore such examples are not included in the guideline.

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		treatment resistant. However, for some reference mAbs clinical conditions may exist where such studies are feasible." However, later on, in chapter 5.3 on Clinical Efficacy it is stated that „The safety of patients should not be compromised by a biosimilarity exercise, and patients should only be treated as medically indicated." There seems to be contradicting statements and a clarification of this possible contradiction is requested.	Nevertheless they may exist. The proposal is written from a scientific perspective in order to allow for such scenarios. The short-comings are acknowledged and also mentioned in the guideline text. The applicant should justify if such low-dose scenario can feasibly be employed without safety or efficacy issues.
308-311	1	Comment: There is no evidence at all of sensitization by pretreatment of any therapeutic proteins (it has been studied with Epo's and the different alpha and beta interferons!). In addition, in other guidelines the MABEL approach is requested without any concern of sensitization, even in patients. Proposed change (if any): Delete the sentence	Not accepted. This sentence allows a fair representation of pros and cons to this approach (please see other comments made by stakeholders). Evidence from erythropoietins and interferons may not be readily extrapolated to mAbs, especially those with higher immunogenicity. As regards the MABEL approach, this situation is different, since patients are tested in a pre-phase I setting, and it is not yet established if the mAb tested will derive any benefit at all. This is in contrast to a situation where a mAb is licensed in a clinical indication with apparent benefit.
308	22	**Comment:** The Guidance states, "Thus, PD data from lower dose(s) may, in principle, provide already pivotal information for the biosimilarity exercise." It is suggested that the most relevant assessment relates to the steepest part of the dose-response curve (most sensitive part of the curve) instead of a "lower dose," which may not be sensitive. Further, we suggest clarifying the word "pivotal." Is it being recommended	Partly accepted. The text has been amended.

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		that PD based on a lower dose is adequate to support registration of a biosimilar? This might be relevant with regards to a prediction of similar efficacy profiles in some situations, but would not appear to be sufficient for a comparative evaluation of safety or immunogenicity under the most sensitive conditions. **Proposed change:** We suggest the alternative language, "**Thus, PD data from the steepest part of the dose-response curve may provide the most relevant information for the biosimilarity exercise**."	
309 - 310	4	Comment: There is no evidence at all of sensibilisation by pretreatment of any therapeutic proteins (it has been studies with epo's and the different alpha and beta interferons!) Proposed change (if any): Delete the sentence	Please see similar comment above.
312	2	Comment: "Such studies" should be more precise Proposed change (if any): "Such studies with clinically relevant PD marker"	Not agreed, since the whole scenario is meant (including lower doses to be tested).

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312-313	20	Comment: If PD comparability is to be tested, need to have some knowledge about sensitivity of marker in order to detect small changes, whether the marker is measurable with acceptable precision etc. Also, whether more than one PD marker is preferred. Specific recommendation for equivalence criteria should be provided here.	The guideline has been revised with as much as specific recommendations as possible in the view of BMWP for a general guideline on biosimilar mAbs.
314-317	2	Comment: Proposed change (if any): Move the sentence to 304 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.	Agreed. This has been considered for the final guideline..
321-324	21	**Comment:** "If 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."	Please see response to comments elsewhere in this document.

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		Efficacy and safety similarity should be established by default as PK/PD similarity does not always translate into efficacy and safety similarity. It is not uncommon that a "highly sensitive" PD marker is not "clinically relevant". If a validated surrogate PD endpoint is available (eg: BP drop, HbA1c), then they provide confidence related to clinical outcome. In such cases, similarity can be partially assessed based on that PD endpoint. It should be the biosimilar mAb manufacturer's responsibility to justify the PD marker and prove the PD sensitivity for the biosimilar mAb. In addition, human comparative pre-licensing safety data are always needed, it is unclear from the text, please revise. The Phase III efficacy/safety studies should be head-to-head comparative studies of the biosimilar against the reference product. The study should be designed as an equivalence study rather than as a non-inferiority study, since the latter would not rule out superiority which could lead to different safety and efficacy profiles. The duration of a comparative study addressing the safety of the biosimilar including immunogenicity could range from 6-12 months or more with the length driven in part by the need to achieve sufficient exposure to assess immunogenicity and to better allow the potential emergence of safety signals.	The text has been revised to be clearer. This is covered in lines 392-394 (published draft), therefore superfluous. Please see discussions elsewhere in this document. Scenarios may exist where non-inferiority is an option. This has also been extensively discussed at the biosimilar mAbs workshop in October 2011 at EMA. Non-inferiority vs equivalence will also be part of the considerations to be made for the revision of the non-clinical and clinical biosimilar guideline, since this is not restricted to biosimilar mAbs. The text on immunogenicity has been revised. Please see comments elsewhere in this document.

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		Immunogenicity must be assessed in head-to-head clinical trials for each biosimilar product. **Proposed change (if any):**	
315-324 321-324 328-330	10	Comment: The guidelines refer to the importance of PD markers for clinical comparability and consider situation where CHMP guidelines for clinical requirements may not strictly need to be applied in order to establish biosimilarity: 1. The guidelines consider that highly sensitive PD studies can show clinical comparability. Lines 328-330 also refer to possible deviations to CHMP clinical guidelines. 2. The guidance recognise that defining an appropriate equivalence margin for establishing equivalent efficacy based on PD markers than on clinical endpoints may be very challenging, and applicants will have to provide reassurance that all relevant aspects of a biosimilar mAb as regards similar clinical efficacy are covered, and where different mechanisms of action are relevant for the claimed indication(s) of the reference product, or	The BMWP considers that the argumentation put forward by past cases where a negative opinion was adopted by CHMP (or an application was withdrawn) can also be seen as examples where the overall data to support biosimilarity, especially (but not restricted to) analytical, physicochemical and biological characterization, showed more than non-significant differences. To replicate the trials made with the reference medicinal product, i.e. to have stand-alone developments, would not yield in comparative data, which would not be a desirable situation. It should be remembered that for the situation where PD markers provide pivotal evidence (should these situations exist) there is still the need to reassure on equivalent safety (Please see lines 392-394 of the draft guideline).

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000585/WC500070792.pdf>

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		uncertainty exists, applicants should provide relevant data to cover pharmacodynamics for all claimed clinical indications (lines 315-317). 3. Lines 321 to 324 state that 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. In terms of regulatory science, relying on PD markers for mAbs is creating a complex situation as it may lower the bar in terms of trial designs needed to firmly establish similarity of efficacy and safety. Comparative trials to establish similarity of efficacy and safety are needed and can require a large number of patients. Although efficacy of a biosimilar mAb *per se* would be expected, it might not always be comparable to that of the reference product. Product attributes like impurities and micro-heterogeneities can have an impact on efficacy and, equally important, safety. Thus, even in cases where a well-established potency assay exists that correlates with clinical efficacy, human data are critical for the development of biosimilar mAbs. The guidelines should not create a framework where human	

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500067088.pdf>

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		PD data would be proportionally too important to establish similarity compared to comparative trials for claims of efficacy and safety, or considered surrogates of clinical similarity. The clinical study requirements to demonstrate similarity is a critical element for any biosimilar product, but it is even more critical with regards to mAbs, and the clinical program is more complex to design than that of common biosimilars. There is no surrogate marker to standardise the development of biosimilar mAbs, and clinical results of the reference product will always depend on how close the clinical development for a biosimilar can be to the original pivotal studies. The demonstration of clinical similarity may require following strictly the same design of the pivotal study of the reference product, and using clinically relevant endpoints instead of surrogate markers. The efforts to develop Biosimilar mAbs are not comparable with those required to develop common biosimilars. Examples of clinical issues to date, which justify a strict plan to demonstrate the benefit risk of biosimilar products and anticipating the requirements for complex products like mAbs, are as follows: • In the case of interferon alfa, the CHMP could not conclude on the comparability of the applicant product versus the reference product because of differences in clinical comparability between the applicant product and the reference product. There was a situation with	

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		clinically and statistically significant difference in virological relapse rates found between the end of therapy and the end of the observation period, inconclusive data in the response rate for a defined population of patients (the "difficult-to-treat" genotype 1 patients), different rate of adverse events and the laboratory-related events judged as clinically relevant, inadequate immunogenicity documentation because of the incomplete validation of the assays and methods used (and the consequent insufficient exclusion of false negative results and the factual differences observed in the detection of anti-interferon antibodies)[16]. • In other cases (insulin and interferon beta), the CHMP had concerns and was of the provisional opinion that insulin products could not have been approved for the treatment of diabetes mellitus. The main concerns of the CHMP were that the comparability between the applicant products and the reference products had not been shown. The studies in healthy volunteers did not show that the applicant products had the same effect in lowering blood sugar levels as the reference product, and the main study showed a trend in favour of the reference product. The CHMP was also concerned that the company had not supplied enough information	

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		on how the active substance or the finished products are made, and that the processes used to make them had not been validated. At the time of the withdrawal, the CHMP's view was that the applicant products could not be considered as biosimilar to the reference medicinal products[17]. • The CHMP also evaluated an application for interferon beta-1a and gave a negative opinion. The company had requested a re-examination of the negative opinion, but this re-examination had not yet finished when the company withdrew the application. At the time of the withdrawal, the CHMP recommended that the marketing authorisation be refused for the treatment of relapsing-remitting multiple sclerosis. The CHMP noted that there were differences between the active substance in the application and other interferon beta-containing medicines available on the market. It therefore concluded that using the published studies on these interferon beta-containing medicines to support the use of the applicant product was not justified, and that studies on the applicant product itself were required. The CHMP was also of the opinion that the results of a single pivotal study in the application did not show enough evidence that the medicine was effective. Based on the information presented to the Committee,	

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		it was not clear whether this was due to the way the study was designed, the way the results were analysed, or to the medicine itself. At the time of the withdrawal, the CHMP was of the opinion that the benefits of the applicant product in the treatment of patients with relapsing-remitting multiple sclerosis did not outweigh its risks[18]. Proposed change (if any): Propose that the demonstration for efficacy and safety be based on study design identical to the pivotal trial for the reference product.	
316-317	20	Comment: Please provide clarity around what would constitute "*relevant data*" to cover for all indications	This will depend on the overall dataset and the scenario.
320	22	**Comment:** We suggest that this section emphasise that superiority (so called "biobetters") is not an acceptable outcome upon which to conclude biosimilarity.	Please see comments elsewhere in this document.
321	2	Comment: See general comment	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
321	10	Comment: Suggest adding sentence below to provide further clarification. Proposed change (if any): "there will be situations in which the disease area in question does not yet know which are the most appropriate and clinically relevant biomarkers, surrogate endpoints, PD markers of interest, and putative mechanism of drugs being studied. Under such circumstances, it will be generally required that efficacy equivalence between innovator and biosimilar products be established through clinical endpoints that have received widespread therapeutic area and regulatory acceptance in the past."	Please see comments elsewhere in this document.
321 - 320	4	Comment: So no human efficacy data necessary if PD studies can be performed? E.g. with Rutiximab?	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
321-324	22	**Comment:** We ask that further clarity be provided on the phrases "highly sensitive" and "clinical relevant." The Guideline should specify equivalence or non-inferiority, and indicate how much room there is to use surrogate PD markers of activity and for what duration. The equivalence trial design must be strongly favored. Should applicants believe that there are special circumstances that justify the use of an non-inferiority design, they should be required to provide robust justification to support this. Such circumstances will be rare.	Please see comments elsewhere in this document.
321-324	5	Comment: Lines 321-324 essentially state that if reliable PD studies cannot be completed, clinical efficacy trials are required. This seems to represent a shift in presumption. The general non-clinical and clinical biosimilar guideline states instead that clinical efficacy trials will usually be necessary to establish biosimilarity. Proposed change (if any): ~~"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~~ **Similar clinical efficacy between the biosimilar and the reference product must** be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), ~~preferably~~ double-blinded ~~and normally equivalence trials.~~ **and with equivalence**	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		margins, unless dose comparative and highly sensitive PD studies convincingly show comparability in a clinically relevant manner."	
321-324	7	Comment: The guideline seems to imply that the completion of (one or two) comparative Phase III trials may not be necessary for authorisation of some biosimilar products. Although the rationale behind this is partly described, depending on the circumstances, a number of points should also be taken into consideration with regard to that scenario. Firstly, the PD markers should be based on the highest possible level of correlation ('level one' evidence) with the clinical outcome and not solely on the mechanism(s) of action. Ideally, both markers should be employed. Secondly, the comparability PD exercise should be based on more stringent interval margins compared to the PK exercise. As a consequence, it should include a	Please see comments elsewhere in this document.

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		larger number of patients compared to a normal bioequivalence study required for a biosimilar product undergoing one or more Phase III trials. Thirdly, further emphasis on post authorisation monitoring should be considered in the development of the pharmacovigilance plan.	
321-324	8	Comment: While dose comparative and sensitive PD studies will surely help in the comparative study, we feel that they should not replace the adequately powered, randomised, parallel groups comparative trial. Indeed, the presence of the clinical study has been the strength and innovation of the first guidelines, and this should therefore remain mandatory. Proposed change (if any): Remove "If dose comparative…..relevant manner".	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
321-324	15	Comment: From the guideline, it appears that the completion of one or two comparative Phase III trials may not be necessary for authorization of some biosimilar products. Although the reasons behind this may be understandable, depending on the circumstances, a number of other considerations not mentioned in the guideline should also be taken into consideration with regards to that scenario. First, the PD markers should be based on the highest possible level of correlation (level one of evidence) with the clinical outcome and not solely on the mechanism(s) of action. Ideally, both markers should be employed. Second, the comparability PD exercise should be based on more stringent interval margins compared to the PK exercise. As a consequence, it should include a larger number of patients compared to a normal 'bioequivalence' study required for a biosimilar undergoing one or more Phase III trials. Third, the number of patients which may be eligible for treatment after the marketing authorization of the biosimilar should be taken into account and considered in the development of the post-marketing pharmacovigilance plan.	Please see comments elsewhere in this document (this is a repetitive comment).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: The draft guidance notes that trials assessing similarity in efficacy would normally be equivalence trials. We believe that some additional discussion of the choice between non-inferiority (NI) and equivalence trials is warranted. In practice, most biological products fall into one of two pharmacodynamic classes, those with a dose response on both sides of the approved dose (or dose range) and those that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect. Cytokines generally fall into the former class. For these products, equivalence (two sided test) should be the standard clinical trial design, as efficacy greater than the reference product is feasible and would be of clinical concern. In the case of the latter class, the target has generally been completely biologically neutralized at the approved dose. Most oncology antibodies and many anti-cytokine antibodies are in this class. For this class, non-inferiority clinical trial designs should be justifiable, as pharmacodynamic activity above the level of the reference biological product is considered as highly unlikely from a biological perspective and would often be of limited clinical concern. For such products, a one-sided NI approach should be acceptable, as studying doses lower than are approved will often be clinically	Agreed. This is already covered by the phrase "normally equivalence trials", which opens the possibility for non-inferiority trials if well justified. This appears to remain the best approach consideringthe conflicting comments (either asking for equivalence trials only, or for requesting opening up more for non-inferiority).

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		infeasible, and given that increased therapeutic activity would not likely be detectable in a feasible therapeutic setting. In such cases, the possibility that the product has greater specific activity than the reference product will need to be addressed by other means. Proposed change: "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 ***either*** equivalence ***and/or non-inferiority trial(s)***. ***Whether an equivalence or non-inferiority trial is most appropriate will need to be determined on a case-by-case basis. If the reference product is approved at a dose away from the top of the dose-response curve, or if it is feasible to study the drug at such a dose, an equivalence trial would normally be most appropriate. If, however, the reference product is approved only at a dose close to saturation, non-inferiority trials may be more appropriate.*** With regard to the specific issues with equivalence ***or non-inferiority trials***, . . ."	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
321-324	20	Comment: Normally, similar clinical efficacy between the biosimilar and reference product should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably in a double blind and usually an equivalence trial. PK/PD similarity does not always translate into efficacy and safety similarity. It is not uncommon that a "*highly sensitive*" PD marker is not "*clinically relevant*". If a validated surrogate PD endpoint is available (e.g. BP drop, HbA1c), then they provide confidence related to clinical outcome. In such cases, similarity can be partially assessed based on that PD endpoint. Only in the case that a PD marker is a validated and recognized regulatory endpoint for the approval of a product in the studied indication can it be used for the primary evaluation of similarity. As indicated above normally equivalence trials are required to establish similarity of the biosimilar product and reference product but in some cases the developer of a biosimilar product may justify the use of a non-inferiority design based on for example: Molecules with a dose response that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect. In these cases pharmacodynamic activity above the level of the reference biological product is considered as highly unlikely from a biological perspective and would often be of limited clinical	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		concern. In such cases, the possibility that the product has greater specific activity than the reference product will need to be addressed by other means. In the case of a non-inferiority trial in addition to meeting the pre-specified non-inferiority margin a second test (hierarchical) for superiority of the biosimilar to the reference product should be carried out. In the case where the non-inferiority margin is met but the biosimilar product is shown to be statistically superior to the reference product similarity would not be established. In this example, the product would need to demonstrate patient benefit/risk and meet appropriate endpoints such as PFS and OS (for oncology trials). Proposed change: "~~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.~~ Normally, similar clinical efficacy between the biosimilar and reference product should be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably in a double blind and usually an equivalence trial as PK/PD similarity does not always translate into efficacy and safety similarity. Only in the case that a PD marker is a	

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		validated and recognized regulatory endpoint for the approval of a product in the studied indication can it be used for the primary evaluation of similarity. As indicated normally equivalence trials are required to establish similarity of the biosimilar product and reference product but in some cases the use of a non-inferiority design may be justified. In the case of a non-inferiority trial, in addition to meeting the pre-specified non-inferiority margin a second test (hierarchical) for superiority of the biosimilar to the reference product should be carried out. In the case where the non-inferiority margin is met but the biosimilar product is shown to be statistically superior to the reference product similarity would not be established. These studies to establish similarity should also include immunogenicity and pharmacokinetic measurements - to assess the effects of immunogenicity on pharmacokinetics, efficacy and safety and need to be long enough to adequately assess these effects.	
321-325	7	Comment: Although the draft guideline states that trials assessing similarity in clinical efficacy would normally be equivalence trials, we believe that some additional consideration of the choice between non-inferiority and equivalence trials is warranted. In practice, most biological products fall into one of two pharmacodynamic classes, those with a dose response on both sides of the approved dose (or dose range) and	Please see comments elsewhere in this document (this is a repetitive comment).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		those that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect. Cytokines generally fall into the former class. For these products, equivalence (two sided test) should be the standard clinical trial design, as efficacy greater than the reference product is feasible and would be of clinical concern. In the case of the latter class, the target has generally been completely biologically neutralized at the approved dose. Most oncology antibodies and many anti-cytokine antibodies are in this class. For this class, non-inferiority clinical trial designs should be justifiable, as pharmacodynamic activity above the level of the reference biological product is considered as highly unlikely from a biological perspective and would often be of limited clinical concern. For such products, a one-sided non-inferiority approach should be acceptable, as studying doses lower than are approved will often be clinically unfeasible, and given that increased therapeutic activity would not likely be detectable in a feasible therapeutic setting. In such cases, the possibility that the product has greater specific activity than the reference product will need to be addressed by other means. Proposed change: "If dose comparative and highly sensitive PD studies cannot be performed convincingly showing	

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		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 **either** equivalence **and/or non-inferiority trial(s)**. **Whether an equivalence or non-inferiority trial is most appropriate will need to be determined on a case-by-case basis. If the reference product is approved at a dose away from the top of the dose-response curve, or if it is feasible to study the drug at such a dose, an equivalence trial would normally be most appropriate. If, however, the reference product is approved only at a dose close to saturation, non-inferiority trials may be more appropriate.** With regard to the specific issues with equivalence **or non-inferiority trials**, …"	
321-355	17	Comment: The first sentence of this section implies that a biosimilar mAb can be approved without a Phase III study; however, it is unclear if this is the guidance EMA wants to communicate and under what conditions. Proposed change: It is recommended to modifying the wording starting on Line 321 to read: "If dose comparative and highly sensitive PD studies ~~cannot be performed convincingly~~	Please see comments elsewhere in this document. The final text has been revised considering all comments made, some supporting the use of PD markers, others requesting clinical efficacy and safety studies in any case.

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		~~showing comparability in a clinically relevant manner~~ **can be performed, the need for further demonstration of comparability through Phase III clinical studies may not be required. If not, similar clinical efficacy between the biosimilar and reference product should be established by** adequately powered, randomised parallel group comparative trial(s)……"	
324	8	Comment: Equivalence trials should be preferred to non-inferiority trials. Indeed, the absence of double-blinded protocols or equivalence trials should be justified. Proposed change: Remove "normally". Add a new sentence: The use of non-inferiority protocols or the absence of a double-blind procedure should be adequately justified.	Please see comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
324	17	Comment: In case of biosimilar developments, demonstration of equivalence is needed for some indications where the desired therapeutic effect range is pre-determined. However, for oncology indications or in the case of autoimmune diseases proof of non-inferiority seems to be also acceptable. Although, it could be argued that proof of non-inferiority would not exclude superior efficacy, in the aforementioned indications such situation would not only be acceptable but beneficial for the patients without posing additional risk, provided that comparative safety is maintained and demonstrated. If non-inferiority design was used in such indications, scientifically no argument is seen for the necessity of the exclusion of potential superiority of biosimilars and for the demonstration of strict two-sided equivalence instead. Nevertheless non-inferiority trial designs would require fewer patients in the comparative clinical studies than equivalence trials and it is thought to be unethical to dose more patients in a biosimilar development than scientifically necessary. It has to be highlighted that biosimilarity is claimed on the basis of thorough comparability program (quality, non-clinical and clinical), and the results should be assessed in that context. Therefore, provided that high level of similarity in the physicochemical and biological properties, and comparability of PK/PD have been demonstrated, non-inferiority designs may be appropriate to confirm clinically relevant comparability,	Please see comments elsewhere in this document. The final wording is the most appropriate approach considering comments either requesting or denying the option for non-inferiority trials.

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		since besides excluding inferiority it can be expected that the biosimilar will not be superior to the reference product either. Consequently, the concept of similar medicinal product development would not be compromised by the non-inferiority design if it would be assessed within the context of the whole data package on comparability. Comment: See comment for line 62- 64 Proposed change: ~~normally~~ equivalence **or non-inferiority** trials.	
324-325	16	Comment: The current draft guideline mentions that "normally" equivalence studies need to be performed for demonstration of clinical comparable efficacy. This leaves the possibilities for other designs open. Specifically, non-inferiority may be considered. Proposed change (if any): A non-inferiority design may be used to demonstrate clinical similarity between the biosimilar and the reference product. Superior efficacy cannot be ruled out in a non-inferiority design. However, when physicochemical, biological (potency), non-clinical comparability data and clinical pharmacokinetic data all demonstrate that the biosimilar is highly comparable	This has indeed been the intention. Please see comments elsewhere in this document.

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		with the reference product, it is very unlikely that the biosimilar would have better efficacy in the clinical setting. In these cases, a non-inferiority design may be proposed and discussed on a case by case basis.	
325	17	Comment: We should be more specific here Proposed change: With regard to the specific issues with **typically** equivalence **or, if justified appropriately, also non-inferiority** trials….	Please see comments elsewhere in this document.
325-326	3	With regard to the specific issues with equivalence trials, e.g. assay sensitivity, reference is made to guidance ICH E10 and the "Guidance on the choice of the non-inferiority margin". "Guidance on the choice of the non-inferiority margin" mentioned that "In general, when there is only one endpoint and one dose of the test treatment, a planned NI study can be tested for superiority without a need for Type I error alpha correction". Please clarify whether this criterion will be applied to the biosimilar trial(s) or not. For example, if the biosimilar trial was designed to show equivalence and achieves biosimilarity in PK/PD, assay sensitivity etc. but shows superiority in the primary clinical endpoint, can superiority be claimed as well?	Please see comments elsewhere in this document. Superiority would formally contradict the character of a biosimilar.

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328	2	Comment: See comment to 65	Not accepted. Please see argumentation in the guideline.
328-329	22	**Comment:** The Guidance states, "deviations from these guidelines (choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc.) may be warranted." This text suggests flexibility on these points without providing the criteria for such flexibility. **Proposed change:** We ask that further clarity be provided on circumstances where deviation may be tolerated and what cumulative limits exist for such deviations.	Not accepted. Deviation from the guidelines may be necessary, e.g. when the usually recommended primary endpoint is influenced by other factors rather than differences between biosimilar and reference medicinal product. This is further discussed in lines 359ff (draft guideline) for anticancer mAbs. It is impossible to provide cumulative limits in a guideline of this format.
328-331	20	Comment: Patient benefit / risk assessment is at the heart of any newly approved product including biosimilars. Regarding the use of response rate as a primary endpoint for assessing biosimilarity for MAbs in oncology indications, with a time-to-event endpoint such as PFS or OS as a secondary endpoint, the guidance should make clear that any evidence that responses are not durable or lead to clinical benefit in these situations should lead to the conclusion that biosimilarity has not been achieved. Even the potential for use of response rate as a primary endpoint for	Not accepted. Benefit has already been established by the reference medicinal product, the biosimilar design follows the principle of establishing biosimilarity. The usually requested endpoints like time-to-event endpoints are included in order to accumulate more data, but the guideline acknowledges that any differences would have to be interpreted with caution. BMWP considers that the current guideline text reflects this, and that an addition of "regulatory accepted endpoints" etc. would not add significant information.

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		demonstrating biosimilarity should only be considered only where such endpoints are validated as acceptable surrogates for clinical benefit in any particular oncology indication. For any indication, use of a surrogate endpoint should always be contingent on there being a validated, scientifically acceptable and regulatory accepted endpoint for a product being developed for the studied indication. Proposed change: "However, to establish biosimilarity, deviations from these guidelines (choice of endpoint, time point of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. ~~Such deviations need to be fully scientifically justified.~~ To establish biosimilarity the primary endpoint chosen should always be contingent on there being a validated, scientifically acceptable and regulatory accepted endpoint for a product being developed for the studied indication."	
330 - 331	3	Comment: " ... include the usually recommended endpoints for a certain condition as secondary endpoint" Proposed change (if any): please clarify whether equivalence needs to be demonstrated for the usually recommended endpoints as well as the primary endpoint.	Acknowledged. The text has been slightly amended.

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331	2	Comment: Usually recommended is unclear Proposed change (if any): The endpoints used for authorisation of the reference product	Not accepted. It is rather the endpoints recommended by current CHMP guidance that are mentioned in the text only a few lines before, therefore no revision of the text is warranted.
331	7	Comment: If the "usually recommended endpoints" are included as secondary endpoints, but are not available until post approval, guidance should be given as to the intended regulatory consequence of a 'negative' outcome and the worth of the evaluation if the study does not show a benefit in these measures.	Not accepted. This has not been included in the guideline, since this would pre-empt a CHMP decision in an individual case.
332	2	Comment: "Acceptable interim endpoint……" followed by "However, such data would have to be interpreted with caution" … is not very clear information for the applicant. Proposed change (if any): To give more precise information: If data are submitted on an acceptable interim endpoint such as a validated surrogate biomarker, and the classical endpoint used for licensing the surrogate can not be demonstrated in the timeframe of the study, data on this endpoint should be gathered in a study extension.	Not accepted. What is meant is that data, e.g. on overall survival or other endpoint data, would have to be assessed having in mind e.g. that the trial may not be powered to detect a small difference (but be powered to fully establish biosimilarity in the primary endpoint). However, there are numerous scenarios for this, and therefore the text has to be kept general.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
332-333	20	Comment: If the recommended endpoint is not tested, there may not be sufficient assurance that the biosimilar applicant has demonstrated efficacy. We do not find it acceptable that data which "would have to be interpreted with caution" form the basis for approval. Proposed change: ~~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.~~ Any alternative endpoint would have to be validated and accepted by regulatory authorities as an appropriate endpoint for registration of any product tested in the studied indication.	Not accepted. Please see similar comments elsewhere in this document. The basis for approval is a firm establishment of biosimilarity with the overall data package, which includes sufficient reassurance as regards equivalent/similar efficacy. Data "to be interpreted with caution" is not the basis for approval, but only a part of the overall data package on which the decision to license a biosimilar mAb is based.
332 - 334	5	Comment: Guideline § 5.3 states that in some cases, an applicant could use "an acceptable interim endpoint for licensing," with data on the usually recommended endpoint to be gathered in a post-authorisation setting, "where	Not agreed, since such scenarios may not always be feasible or necessary, depending on the mAb and its data package. Nevertheless, the basis for approval is always a positive benefit-risk for a biosimilar mAb, supported by unequivocally

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		feasible and considered necessary." We agree that it may be appropriate in some instances to approve a biosimilar on the basis of an interim endpoint. There should be a compelling scientific basis for concluding that the interim endpoint will be predictive of the actual recommended endpoint, however, and the applicant should in every case gather data on the usually recommended endpoint after approval. If gathering these data would not be feasible, the product should not be approved on the basis of the interim endpoint. Proposed change (if any): ~~"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.~~ **In some cases, it may be acceptable to use an interim endpoint for licensing, provided there is compelling evidence that the endpoint will be predictive of the usually recommended endpoint. In such a situation, data on the usually recommended endpoint should be gathered in a post-authorisation setting. These data would have to be interpreted with caution, due to numerous influencing factors and likely imprecise estimates."**	established biosimilarity. Therefore, no change is necessary to the guideline text.

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332 - 334	6	Comment: „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." Proposed change (if any): This option should be deleted since it appears to create regulatory standards for biosimilars which are certainly not in the interest of the patients.	Please see comments elsewhere in this document. It is not clear why the regulatory principles established in this guideline would not be in the interest of the patients.
332-334	21	**Comment:** "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-authorization setting, where feasible and considered necessary." How is an "acceptable interim endpoint" determined? Only valid endpoints should be used as primary basis of approval of any product. It is not agreed that biosimilars should be approved via "conditional pathway", i.e. based on the post-approval data. There is no unmet medical need provided respective innovator products/ prior approved	Not accepted. BMWP recommends keeping the following scenario: depending on the data, a biosimilarity endpoint forms the basis for approval, and the usually recommended clinical endpoint is gathered post-approval, if feasible and necessary. The CHMP opinion on a MAA will be based on the data submitted by the Applicant. The guideline should not pre-empt any decision of the CHMP since each product is evaluated based on the data package provided.

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		biosimilars are on the market. However, it is worth keeping in mind that even post-authorisation, RCTs should still be possible. **Proposed change (if any):** Remove the proposed approach	
333	10	Comment: Suggest adding sentence below to provide further clarification. Proposed change (if any): "In situations whereupon an interim analysis is proposed to support comparability, strong justification should be provided to support the notion that such interim, shorter-term endpoints carry similar clinical meaningfulness as more traditional longer-term endpoints that may have been employed by previous innovator products."	Not accepted. Please see comments elsewhere. It is not the clinical meaningfulness, but the establishment of biosimilarity which is the primary objective. Clinical meaningfulness has been established by the reference medicinal product.
334–336	3	Comment: Data gathered in post-authorisation setting. It is worth keeping in mind that even post-authorisation, RCTs should still be possible. Although they are costly and put burdens on patients, given that the treatments being compared are assumed to give the same effects, many of the difficulties of RCTs post-authorisation do	Such studies would certainly become necessary should CHMP see the need for further confirmation of biosimilarity after authorisation. However, this is a CHMP decision and not meant to be a default scenario.

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		not hold.	
337-348	21	**Comment:** "Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not), and.." It is not understood how not licensed conditions could be used. If biosimilarity is demonstrated in an unlicensed indication, and there are no data for the reference product in this indication, how can the regulators assume clinical efficacy for the biosimilar? This is also in contradiction to the statement on line 248 : "The safety of patients should not be compromised by a biosimilarity exercise, and patients should only be treated as medically indicated." (This statement may be regarded partly against the use of healthy volunteers, too?). Consider also ethics of such an approach?	BMWP strongly recommends that in such scenario the applicant seeks a scientific advice procedure upfront. The reasoning for this scenario is that if there was, in theory, a very sensitive model which is widely used in the medical community (based, for example, on publications of study data peer-reviewed journals) but not formally licensed, then this could (pending agreement with regulatory authorities) be considered as a possible model from a scientific perspective. PK data etc. would be generated in a comparative manner, and therefore would become available with the biosimilar mAb MAA submission. As regards the safety discussion, it is not clear why it would be regarded against the use of healthy volunteers, which would not be a different scenario compared to any phase I study in healthy volunteers. This is out of the scope of this guideline since this not specific to biosimilar mAbs.

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		In addition, to our understanding a biosimilar can get all or part of the reference product indications, not more. **Proposed change (if any):** Remove "(whether licensed or not)", or provide sufficient justification and explanation on the acceptability of such an approach.	Not accepted. The wording has been kept based on the above considerations.
337-338	2	Comment: This an introductory sentence and here misplaced. Rather contradictory elements should be deleted Proposed change (if any): Delete (whether licensed or not) replace "that the model is Comment: relevant and sensitive" by "its approach"	BMWP does not see a contradiction here. Please refer also to comments made above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
337-338	7	Comment: This paragraph is open to misinterpretation by developers of biosimilar products, especially with the inclusion of the wording "(whether licensed or not)" at line 338. This is contradicted later by use of the wording "as medically indicated" at line 348. The concept of demonstrating similarity to an unapproved indication/condition and relying on this as pivotal evidence for approval of the biosimilar may not have legal basis in Europe. It is recommended that the language is strengthened to provide legal certainty and clarity for all stakeholders.	Please see above.
337-338	17	Comment: The wording in Lines 337-338 is confusing, "Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not), and…" It is recommended to clarify the statement "whether licensed or not," i.e. does this mean a sensitive indication can be studied even if it is not approved for the reference product?	Please see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
337-339	5	Comment: Guideline § 5.3 states that biosimilarity "should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not)." We are concerned about the reference to unlicensed study conditions because it seems to tacitly approve of administering a product under unlicensed conditions, but does not provide further clarification, thus creating the potential for serious safety and other problems. Proposed change (if any): "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."	Please see above.
337 - 339	6	Comment: „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." Proposed change (if any): Since this would imply that the reference product is	Please refer to the similar comments made elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		used in such a comparative trial outside its licensed indication, this option should not be provided in the guidance given that the premise is that no patients should be put at risk in testing a biosimilar. Further comments: • It should be made clear that PK/PD studies alone can only exceptionally provide sufficient data to demonstrate similarity. • Comparative equivalence trials should be considered the normal route for investigating similarity. At present, there are no validated in vivo PD surrogates for mAbs approved in oncology or rheumatoid arthritis to mention just two important disease areas. • Typically, comparability of biosimilar and innovator mAb should be demonstrated in a head to head phase 3 clinical study which should also include immunogenicity assessment. These studies need to be adequately long to allow proper assessment of efficacy and safety of the biosimilar product. • If – exceptionally – PD studies alone are allowed to assess efficacy, an additional clinical safety study has to be conducted. This is particularly important because immunogenicity is a key safety factor of all biological products and can only be assessed in clinical trials.	Please see elsewhere in this document. BMWP considers that the guideline is clear in this aspect. Please see guideline text: Safety aspects are mentioned in lines 392-394 of the draft guideline.

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337-339	11	Comment: "most sensitive human models, whether indicated or not". This poses several ethical and clinical problems. What would the availability of literature be if the drug was not indicated? Why would one expect adequate benefit and risk and hence approval by ethics committees and investigators if there was no indication? Wouldn't regulators really prefer data in a population that was likely to use the biosimilar post approval, as compared to a population that does not use the product? Proposed change (if any): Specific consideration should be given to a representative population.	Please see above.
337-339	15	Comment: Product developers may over-interpret the text "whether licensed or not", despite the guidance's efforts (later in this section) to explain that any alternative population or study conditions should be shown to be relevant to the indications applied for. Therefore, the language could be strengthened and made more explicit so as to reduce the potential for over-interpretation. Proposed change: "Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions (whether licensed or not), and the applicant	Please see above.

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		should justify that the model is relevant and sensitive to demonstrate comparability in relation to efficacy and safety in the indication(s) applied for. ***More specifically, if an indication, study population, or study condition is used which is not licensed, then the applicant will need to convincingly demonstrate that the findings are fully applicable to the licensed indication, population, and conditions of use, in terms of PK, PD, efficacy, safety, and immunogenicity findings.***	
337-339	20	Comment: "*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*." We interpret this statement as a proposal to conduct comparative studies in an indication or population for which the reference product is not authorised. This poses several regulatory, ethical and clinical issues. If the reference product does not have the indication approved, the clinical trial would effectively be comparing two investigational drugs. What information would be available to demonstrate adequate benefit and risk and hence support approval by ethics committees and investigators?	Please see comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		How does the regulator assess comparable safety and efficacy to the innovator, if the study is conducted in a population that has not been fully characterized with respect to safety and efficacy by the innovator, through pivotal clinical studies and post marketing experience? Such studies could only be considered as supporting data, as they could not be sufficient to demonstrate biosimilarity. The proposal to permit studies in unlicensed indications contradicts the statement on line 347: "The safety of patients should not be compromised by a biosimilarity exercise, and patients should only be treated as medically indicated." This section also contradicts the EMA Guideline on Similar Biological Medicinal Products, which notes that "The chosen reference medicinal product, defined on the basis of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies during the development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions." If it is intended that the comparative study be conducted in an indication that is not approved for the reference product in the Community but for which there is evidence of well-established use or for which the reference product is approved outside the Community, then these criteria should be explained in the guidance.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is not clear whether, on the basis of such studies, the biosimilar could be accorded an indication that the reference product does not have, and whether as a consequence the innovator could claim similarity and obtain that indication. If not, then it raises the question of whether it would be ethical to conduct clinical trials in a population for an indication when there is no intent to develop the product to benefit that population. Proposed change: Delete "(whether licensed or not)".	Please see comment above.
337-339	22	**Comment:** This section contradicts the EMA Guideline on Similar Biological Medicinal Products (CHMP/437/04), which notes that, "The chosen reference medicinal product, defined on the basis of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies during the development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions." This reference also seems to conflict with the recognition that patients should be treated "as medically indicated." (Lines 347-348) **Proposed change:** We suggest ommiting reference to unlicensed conditions, "**Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~(whether licensed or not)~~...”	
337-348	20	Comment: Even when clinical similarity is assessed using clinical *endpoints, these endpoints may not be sensitive enough to pick up all meaningful differences between the products. Accordingly, the CHMP should require applicants to measure, and demonstrate the equivalence of, pharmacodynamic markers and surrogates, in addition to clinical endpoints. Such markers, even if not validated to predict clinical endpoints, can provide increased sensitivity to clinical differences.* Proposed change: After line 348, the CHMP should insert the following sentence: “Even where an Applicant assesses similarity using clinical endpoints, these endpoints may not be sensitive enough to reveal all relevant differences between the products. In such a case, Applicants may measure, and demonstrate the equivalence of, pharmacodynamic markers and surrogates, in addition to clinical endpoints.”	Partly accepted. The wording has been adapted.
341	17	Comment: During the development process, first, physicochemical similarity is proven; then biosimilarity of biological properties is shown by a broad panel of state of the art	Comments noted, but no change of the text is considered necessary.

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		assays, which cover all possible bindings and mechanisms of action of the mAb. The proved physicochemical and biological similarity, without the interference with disease related factors, can strongly indicate that the reference and the biosimilar mAbs have also similar effects in patients. To prove this, the most sensitive clinical model should be chosen because this model is the most appropriate to show any potential difference in efficacy. Since in different indications the clinical effect depends on the functions of the mAb after the specific binding of the mAb to the same antigen, the extrapolation of efficacy is not expected to be different in less sensitive indications. Furthermore, from safety point of view, differences could be shown best in target populations where adverse events of interest would occur most frequently and the on-target side effects might be easier to recognize in patients with less co-morbidities. Besides these, the most sensitive models are often those that include less immune-compromised patients, thus making them a better target population to detect differences or to show comparability regarding immunogenicity (see also the comment on line 392 regarding extrapolation of safety). In summary, provided that similarity in physicochemical and biological properties have been demonstrated, and biosimilar and reference mAbs show similar efficacy, safety and immunogenicity profiles in the most sensitive clinical model, it is not to be expected that the	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biosimilar and reference mAbs behave differently in other indications for which the reference has been also approved. Comment: It needs to be emphasized again that comparative PD study alone together with sufficient safety data could be able to demonstrate comparability of the biosimilar and the reference product. Well established PD endpoints supported by broad set of comparative *in vitro* assay studies carried out in the non-clinical program would be highly predictive and provide more sensitive tools to assess comparative efficacy in the most sensitive patient population. The *in vitro* assays performed in the non-clinical program cover all possible bindings and mechanism of actions. The only difference across indications is the significance of the different mechanisms (e.g. CDC, ADCC, apoptosis, etc.) in different diseases. Consequently, since the same mechanisms of action apply to other indications and subpopulations of such approved indications of the reference product, the extrapolation of comparable efficacy can be justified.	
341 212	20	Comment: The Agency emphasises the use of a homogeneous trial population for clinical studies. However, such a restricted patient population may not be predictive of post-approval use in the wider population.	Not accepted. This comment is unclear, since the interactions with concomitant medications etc. are not relevant for a biosimilarity exercise; data should already exist from the experience with the reference medicinal product. Therefore, BMWP considers that no change to the text is necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Although a homogeneous trial population may limit noise it may not be representative enough of the treated population to detect differences of the biosimilar in safety and efficacy that can result from interactions due to concomitant medications and varying amounts of immunosuppression. Also, the use of subgroups of patients may be statistically flawed and not validated.	
343	17	Comment: We should be more specific here Proposed change: …..thus the sample size needed to prove **typically** equivalence **or, if justified appropriately, also non-inferiority**, and can simplify interpretation.	Not accepted. While non-inferiority may be an option in a case-by-case basis, subject to adequate justification (please see comments elsewhere in this document), it is preferred not to amend the text here, since it is anyway implicit that if an Applicant can justify equivalence, then this would also be applicable to this particular item.
343-345	21	**Comment:** This refers to possible difference between study treatments in terms of the outcomes and how to interpret them. In this scenario, if we see any differences, then the case for biosimilarity has not been well established, so this is much less of a problem. The problem is that such diversity in the study population reduces study sensitivity. **Proposed change (if any):** suggest delete sentence running from lines 343 to 347.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
343 – 345	3	Comment: This refers to possible difference between study treatments in terms of the outcomes and how to interpret them. In this scenario, if we see any differences, then the case for biosimilarity has not been well established, so this is much less of a problem. The problem is that such diversity in the study population reduces study sensitivity. Proposed change (if any): Suggest delete sentence running from lines 343 to 347.	Partly accepted. The text is revised, but explanations are still kept, since important when reviewing a biosimilar mAb application.
348	3	Comment: Saying that patients should only be treated as medically indicated contradicts options to use healthy volunteers (lines 52 and 214) or in conditions "whether licensed or not" (line 338). Proposed change (if any): Just keep first part of sentence: "the safety of patients should not be compromised by a biosimilarity exercise."	Not accepted. BMWP considers that this is not necessarily a contradiction from a medical perspective, since patients can receive a medicine outside the license but still with medical evidence. Nevertheless, please refer to explanations elsewhere in this document.
349	2	Comment: The term normally is asking for exceptions. If those exist state them. Proposed change (if any): Delete "normally"	Not accepted. The word "normally" implies that Applicants (or Scientific Advice) may identify future scenarios where testing is necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
349	20	Comment: "*Clinical studies in special populations like the paediatric population or the elderly are normally not required…*" This is regarded as a general statement: approval in each population & indication should be carefully justified. It is mentioned in this guidance that patients at different ages may show different PK and respond differently to a biosimilar mAb. There should be a need by default to compare different populations, and the waiver to carry out studies in all target populations should be considered on a case by case basis. It should be clarified if the statement applies universally or exclusively to situations in which the reference mAb is not registered in special populations. If the reference mAb has for example a different safety profile in a special population it could be of importance to test the biosimilar mAb in this population, too. Proposed change: Rewrite. In addition, as the issue concerns also safety, should the whole paragraph be moved elsewhere in the guideline?	Please see comments elsewhere in this document. Some aspects mentioned here may not be relevant for a biosimilar setting.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
349 ff	21	**Comment:** "Clinical studies in special populations like the paediatric population or the elderly are normally not required…" This is regarded as a general statement: approval in each population & indication should be carefully justified. It is mentioned in this guidance that patients at different ages may show different PK and respond differently to a biosimilar mAb. There should be a need by default to compare different populations, and the waiver to carry out studies in all target populations should be considered on a case by case basis. It should be clarified if the statement applies universally or exclusively to situations in which the reference mAb is not registered in special populations. If the reference mAb has for example a different safety profile in a special population it could be of importance to test the biosimilar mAb in this population, too. **Proposed change (if any):** Rewrite. In addition, as the issue concerns also safety, should the whole paragraph be moved elsewhere in the guideline?	Please refer to similar comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
349-350	7	Comment: Whilst particular studies in special populations may not be required the guideline should acknowledge the different metabolism and immune status of children and other special populations as relevant to assessing immunogenicity of mAbs.	Not accepted. This is a detailed aspect that may or may not be relevant for a biosimilar development. It is surely relevant for a new-in-class mAb.
349-352	14	Comment: We support the guideline recognizing the scope of "Regulation EC 1901/2006 on medicinal products for paediatric use" also valid for biosimilar monoclonal antibodies. We concur with the regulation exempting biosimilars and generics from paediatric investigation plans unless these products would seek new paediatric indications or formulations. Proposed change : No changes are recommended	Comment noted.
349-352	22	**Comment:** The Guidance states, "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 text appears to contradict other biosimilars Guidelines, as well as the EMA's draft immunogenicity guideline (EMA/CHMP/BMWP/86289/2010), which recommend	Please refer to similar comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		evaluation of safety and/or immunogenicity in the most sensitive populations. **Proposed Change:** We ask that this guidance be aligned with the EMA's draft immunogenicity guidance (lines 318-321) which recognizes that, "**Children may have higher protein metabolism and a different immune status than adults, and cases are known where data suggest a considerably higher immunogenicity of mAbs. In this patient group immunogenicity should be evaluated separately as for adults.**"	
349 - 352	5	Comment: This portion of § 5.3 notes that because the overall objective of the development program is to establish biosimilarity, the selection of the primary patient population must be driven by the need for homogeneity and sensitivity and studies in special populations will normally not be needed. We agree that relatively homogenous populations will provide the power to show or exclude some of the relevant differences between products. Where there is a significant possibility of product differences that are not manifest in homogeneous populations, however, additional studies in the relevant subpopulations should be required. Consideration should particularly be given to studies in subpopulations that might be especially sensitive to differences between the products, such as elderly and	Not accepted. This may not be needed, since it is implied in the principle to ask for the most sensitive patient population and to justify the overall approach taken. Please also refer to similar comments elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pediatric populations. In this regard, we note that the draft mAb immunogenicity guideline provides specific reasons why immunogenicity may be higher in special populations and why it should therefore be separately evaluated in children. (lines 322-323) Proposed change (if any): "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~~ **should be performed when there is a significant possibility that the population might be more sensitive to potential product differences than the studied homogeneous population. For example, in some cases children may be sensitive to differences in immunogenicity that may not be apparent in adult populations.**"	
349-352	20	Comment: As mentioned above the guideline's emphasis on testing in homogeneous patient populations is warranted in some cases. But the guideline should also address the need for testing in patient subpopulations, for example, where a subpopulation could be particularly sensitive to differences between the products, especially around safety. Indeed, the draft mAb immunogenicity guidance recognizes that immunogenicity can vary	Please see similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		based on factors such as patient age and that immunogenicity should be separately explored in children (lines 322-323). Proposed change: "Clinical studies in special populations like the paediatric population or the elderly are not required **in some cases** 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. **However, if a patient subpopulation is known to present particular risks or where a subpopulation might be more sensitive to differences between the products, Applicants should study these subpopulations as well. In addition, immunogenicity testing in children and other subpopulations will generally be required unless justified. (See Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use § 9.1).**"	
353	21	**Comment: "**The inclusion of patients from non-European countries is generally possible" Because different safety issues can be seen in different regional populations, more detailed guidance on whether studies on biosimilar mAb need to match populations used in reference mAb studies and if populations completely outside EU countries are	This comment will be noted for later revisions and/or new product-specific guidelines, should CHMP considers the need.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sufficient for approval in EEA countries would be helpful and increase transparency. **Proposed change (if any):** Potentially best to be addressed in product specific guidelines?	
353	22	**Comment:** "The inclusion of patients from non-European countries is generally possible." We suggest that it should be clarified if this sentence refers to the biosimilar clinical studies to be conducted or those from the reference product. If the reference product is not licensed by EMA, then how will the EMA leverage any safety or efficacy understanding of the reference product? Is the EC willing to have medicinal products distributed in the Community based on the extrapolation and/or adopt the confirmation without verification of safety and efficacy from a foreign agency? **Proposed Change:** We suggest that the EMA clarify the sentence with regards to the sourcing of the comparator product used in studies conducted in non-European countries.	Not accepted. This sentence refers to patients, not reference medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
353 - 355	5	Comment: These provisions would permit a biosimilar applicant to conduct its clinical trials using patients from non-European countries. We recommend that the guideline make it clear that the applicant bears the burden in this case of demonstrating that the reference product is licensed in the EU. Proposed change (if any): On line 353, add the following sentence: **"The Applicant in this case bears the burden of demonstrating that the reference mAb in these clinical trials is licensed in the EU."**	Please see similar comment above. This sentence refers to patients, and it is assumed that these patients will be treated with the relevant reference medicinal product authorised in the EU.
353-355	17	Comment: The reasons behind the statement "knowledge of efficacy and safety of the reference mAb in a particular region may be necessary to prospectively define an equivalence margin" are not clear. It is recommended that further explanation be provided in the guidance document as to the reasons for this statement.	Accepted. Further explanation is added.
353-355	20	Comment: Lines 353-355 would appear to permit biosimilar mAb applicants to conduct their comparative clinical trials outside the EU. The innovator product licensed in a non-EU jurisdiction may not be identical to the EU	Please refer to similar comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		licensed product. To avoid misunderstanding, the guidance should clarify that the product involved in these trials must still be a reference product licensed in the EU on the basis of a full dossier. Proposed change: "The inclusion of patients from non-European countries is generally possible. **In such a case, the Applicant must demonstrate that the reference product used in the clinical trials is the product licensed in the EU. Knowledge of efficacy and safety of the reference mAb in a particular region may be necessary in order to prospectively define an equivalence margin.**"	
353-356	2	Comment: The first two sentences are unnecessary Proposed change (if any): Delete the inclusion of patients….. … are included"	Not accepted. BMWP considers the sentences necessary.
355	17	Comment: Line 355 states that "Stratification and appropriate subgroup analyses are normally expected…" In general, for patients in different global regions this stratification and subgroup analysis is applied if different treatment strategies (e.g., different dose or different efficacy or safety profiles) are used for different ethnic populations.	Please see comments elsewhere in this document and the final guideline text, especially as regards non-inferiority.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: **"**Stratification and appropriate subgroup analyses are normally expected if ~~patients from different global regions are included~~ **different treatment strategies (e.g., different dose or different efficacy or safety profiles) are used for different ethnic populations."** Comment: We need to be more precise. Proposed change: …..to prospectively define an equivalence **or non-inferiority** margin	
358-385	7	Comment: Section 5.3.1 places an emphasis on confirming similarity and not demonstrating patient benefit. However, it should be noted that regulatory approval will be made on the basis of a positive risk/benefit balance. Even if only PD studies are required they should be sufficiently long to evaluate differences in quality attributes on the safety/immunogenicity profile. In addition, sample size should be sufficient to give an estimate of treatment effect with a confidence sufficient to avoid conclusion of no treatment difference when one actually exists.	BMWP considers the guideline to be sufficiently clear on these aspects. A positive B/R is always required, and in case there is lack of data as described in this comment it will be the totality of evidence that drives the decision towards an approval.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Factors described as influencing sensitivity of the oncology surrogate markers (e.g. tumour burden) are also relevant to the ability to extrapolate across different tumour settings. Finally, if progression free survival or overall survival is measured as secondary endpoint, but not available until after initial approval, clarification is requested on the intended regulatory consequences for lack of confirmed benefit, and therefore whether it should be evaluated.	
358-385	20	Comment: If ORR is the primary endpoint and PFS and OS are also recorded, what are the expectations for the comparisons of these endpoints? What does "*on an exploratory basis*" mean? If used, ORR would need to be a validated endpoint. RR is a PD marker of efficacy but does not inform on safety and this still needs to be considered. PFS has the benefit in that it covers mortal events. If PFS/OS did not correlate (trending in wrong direction compared to the innovator product) then the product is not biosimilar. Any such study would need to adequately power PFS/OS as a secondary endpoint. Given the above, the recommendation is for a complete dataset using validated endpoints, pre-approval. Proposed change: **"**Such endpoints are important to establish patient benefit for a new anticancer drug, but may not be feasible or sensitive enough for establishing	Partly accepted. The text has been updated.. To power a trial for significance in a secondary endpoint may be unfeasible. The interpretation of data is up to assessment, not up to a guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. If ORR is selected, it should be established as a clinically relevant endpoint. If used as a surrogate endpoint for PFS/OS, correlation to ORR should be validated (there maybe situations in which RR does not correlate with e.g. PFS/TTP because of differences in binding pattern/Ag shedding, etc). Divergent results between primary and secondary endpoints where the secondary endpoint is used as the basis for approval for the innovator should lead to a conclusion of non-similarity."	
359	17	Comment: In order to prove similar efficacy in cancer indications, progression free survival (PFS), disease free survival (DFS) or overall survival (OS) seem to be less sensitive compared to tumor response. Such endpoints are important to establish patient benefit for a new anticancer drug, but may not be feasible for biosimilar development where sensitive endpoint is needed to detect potential differences between the biosimilar and reference products. In addition, statistically powered clinical studies to prove PFS/DFS or OS equivalence or	Comment noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		even non-inferiority would results in trials of thousands of patients which would lead to unnecessary exposure of high number of patients to the test drug. Rather, it seems to be more appropriate to measure more sensitive parameters like overall response rate in a homogenous patient population to detect potential differences between the products and not to be compromised by patient or disease related factors. Moreover, based on the physicochemical and biological high similarity it is not to be expected that the biosimilar and originator mAb behave differently in PFS/DFS/OS if ORR/CR are similar.	
360	20	Comment: Extrapolation of safety described here in different disease settings requires careful consideration. It is recommended that there is a stronger link between these sections. It is suggested that the section should more strongly state that different safety profile would indicate lack of similarity and would require specific justification to support continued biosimilarity conclusion. The safety evaluation is also a function of potency, affinity etc as such, molecules should be investigated based on their effect on relevant parameters (immunosuppression, on-target MOA based toxicities; effect on vaccination; development of AI disease or traits etc).	Partly accepted. This is in principle correct; however, differences in safety profile are up to assessment, since such differences could be due to chance (lack of power) etc.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
362-367	21	**Comment:** These are also potential confounders for the innovative products, but nevertheless required (e.g. subsequent lines of treatment for OS), so should not the same apply for biosimilars? **Proposed change (if any):** Please clarify/ reconsider	Not accepted, since the objective of a biosimilar development is different.
364, 364-369	2	Comment: The term not sensitive enough may be misunderstood Proposed change (if any): Delete "or not sensitive enough".. delete of a biosimilar mAb to a……and the reference mAb."	Not accepted. It is not clear to BMWP why the wording may be misundertood.
370-374	21	**Comment:** The statement that similar efficacy and safety to the reference compound, not patient benefit per se, needs to be shown is very important. This said it will be very challenging to find a sufficient number of patients with homogenous disease criteria especially in the metastatic setting. In addition, while ORR maybe suitable in showing similar efficacy to the reference compound there maybe situations in which RR does not correlate with e.g. PFS/TTP because of differences in binding pattern/Ag shedding, etc. Therefore, the importance of recording time-dependent EP data (not necessarily OS) is critical and should be highlighted. As this subject is particularly important for the adjuvant	Not accepted. BMWP considers that this is still under discussion in the scientific community, and that lack of extrapolation from or to the metastatic setting cannot yet be ruled out or confirmed in this guideline. It is agreed that finding a homogeneous patient population can be challenging. Nevertheless, a guideline usually gives the "ideal" picture on what is ideally recommended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		setting (establishing efficacy in the metastatic setting should not automatically extrapolated to the adjuvant setting) guidance on this situation should be provided in addition. **Proposed change (if any)**: Suggest modification of wording including a clarification how to approach the adjuvant setting (e.g. would similar efficacy based on DFS be required or a neo-adjuvant study be acceptable to bridge to adjuvant?)	
372-374	21	**Comment:** The most sensitive population and most sensitive endpoint will often not be consistent with the registered label of the reference product. Can it therefore be assumed that the basis for registration of the reference mAb is of little or no relevance when establishing similar efficacy and safety of a biosimilar anti-cancer mAb? **Proposed change (if any):**	The basis for registration of the reference medicinal product is relevant insofar as it established the benefit and risk of the particular product. It may be of less relevance as regards aspects of clinical trial design for a biosimilarity exercise. Please also refer to other comments in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
376-382	21	**Comment**: PFS as an endpoint covers the disease progression and any cause of death while ORR covers the changes in the tumour burden. Safety related death does not have impact on ORR thus safety concern is not addressed. Might be useful to take this into consideration. We suggest to measure ORR in case of all claimed indications as a minimum requirement. Beyond ORR other validated efficacy endpoint should be evaluated as ORR results cannot always be extrapolated to PFS or OS results, vice versa. **Proposed change (if any):**	Safety events, including death, are expected to be recorded and will be assessed. As regards validation of ORR, please see comments elsewhere in this document. Correlation to OS may not always be on obstacle to the validity of ORR as an endpoint for a biosimilar.
376 - 384	5	Comment: We agree with the observation in § 5.3.1 that establishing similar clinical safety and efficacy may be particularly challenging in oncology indications. As mentioned in the guideline, the preferred endpoint to establish efficacy is typically progression free survival (PFS) or overall survival (OS). Although it may be acceptable in some cases, as the guideline suggests, to base approval of a biosimilar on a study assessing Overall Response Rate (ORR) in a homogenous population, in some cases, ORR may not be sensitive to	This is an interesting aspect. BMWP considers that such considerations would have to be part of the justification of an applicant explaining the choice of endpoints (which is always required).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		differences that might affect overall survival. For example, some mAbs act both by inducing cell death and by inhibiting cell growth (e.g., via growth factor receptor blockade). Similarity in inducing cell death may lead to a finding of similar ORR, but this finding may fail to reflect differences in growth inhibition that will lead to differences in survival. Accordingly, ORR may be the most sensitive measure for the detection of some differences, but other differences may be revealed only by assessing PFS or OS. In such a case, both ORR and PFS or OS should be measured to ensure similarity of efficacy. Proposed change (if any): The guideline should indicate that in some cases, depending on the mechanism(s) of action of the biosimilar mAb, clinical studies to establish equivalence of PFS or OS in addition to ORR may be required.	
385	3	Comment: There does seem the need for a "well justified" reason to include novel endpoints for exploratory analyses. Whilst there should be some rationale for collecting extra data, the exploratory setting might well be in order to justify use in future. Proposed change (if any): Suggest delete this sentence.	Partly accepted. The sentence has been modified. What was meant was that some new endpoints may be very sensitive and scientifically well suited, even if not "validated", to add a further important detail of information as regards biosimilarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
385	21	**Comment:** "Novel endpoints may be employed on an exploratory basis if well justified (e.g., time to response)." This point needs further clarification and explanation on the benefit in the context of biosimilars. Should "only" be added?: "Novel endpoints may be employed on an exploratory basis only if well justified (e.g., time to response)." **Proposed change (if any):**	Please see above.
385	20	Comment: "*Novel endpoints may be employed on an exploratory basis if well justified (e.g., time to response).*" This point needs further clarification and explanation on the benefit in the context of biosimilars. Proposed change: "Novel endpoints may be employed on an exploratory basis **only** if well justified (e.g., time to response)."	Please see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
385-423	7	Comment: Section 5.4 should emphasise that extrapolation of safety between products requires careful pharmacovigilance beyond routine collection in order to generate indication-specific safety data, and make reference to section 7. The section should more strongly state that a different safety profile would indicate lack of similarity and would require specific justification to support a continued biosimilarity conclusion.	Partly accepted. Additional Pharmacovigilance activities in an indication based on extrapolation should be assessed on a case-by-case basis.
386	22	**Comment:** Extrapolation of safety described here in different disease settings requires careful pharmacovigilance. We suggest that there is a stronger link between these sections. Further, we suggest that the section should more strongly state that a different safety profile would indicate lack of similarity and would require specific justification to support continued biosimilarity conclusion.	Please see response to the comment of stakeholder 7 on this section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
388	21	**Comment:** It is recommended to use the same definitions for safety parameters and additionally safety parameters which were identified during the use of the product on the market. **Proposed change (if any):**	Accepted with minor changes.
388	20	Comment: Additionally, safety parameters which were identified during the use of the product on the market should be used. Proposed change: "It is recommended to use the same definitions for safety parameters and additionally safety parameters which were identified during the use of the product on the market."	Accepted with minor changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
390 - 398	2	Comment: The sentence could be misunderstood as allowance for a small Phase I PK and tolerability study. Proposed change (if any): Add some information where an additional safety study on a specific issue might be required and where such a study may be sufficient for demonstration of biosimilarity. Comment: Usually recommended is unclear Proposed change (if any): Clinically relevant validated surrogate endpoints	Not accepted. In some cases PD studies might be sufficient to show similar efficacy. As stated in the guideline similar safety should then be studied in a sufficient number of patients sufficient to determine the adverse effect profiles and compare this with the reference product. The type of safety study should be decided on a case-by-case basis and no detailed requirements can be given in the guideline.
390-398	11	Comment: comparable safety. Of course the size of any trial comparing safety events will depend on the prevalence of the adverse reaction. But having said that, sponsors would benefit from some direction in terms of safety databases required "in general" Proposed change (if any): Suggest revising the sentence "Prelicensing safety data should be obtained in a number of patients sufficient to determine the adverse effect profiles of the biosimilar medicinal product" to "Prelicensing safety data should be obtained in a number of patients (for example, at	Accepted with minor changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		least 100 patients exposed for a minimum of one-year, according to ICH guidance E1) sufficient to determine the adverse effect profiles of the biosimilar medicinal product."	
392	17	Comment: From safety point of view, the most sensitive models are often those that include less immune-compromised patients, thus making them a better target population to detect differences or to show comparability regarding immunogenicity. Provided that high similarity of physicochemical and biological properties is shown, and after clinical comparability has been demonstrated in one indication which is very sensitive to detect differences, it is not to be expected that the safety profile of the biosimilar and reference mAbs will be different in another indication (see also comment on extrapolation of indications at line 341, 425).	Accepted. However, there might be cases where differences in the safety profile might be expected. Therefore a statement is included in the guideline.
392-394	20	Comment: Studies using PD markers alone can only be used to establish similarity if those PD markers are regulatory recognized and validated endpoints to establish efficacy of the innovator product or have subsequently been accepted as valid endpoints for approval. Comment: The ADA should be monitored in clinical studies for	Please refer to the section on clinical efficacy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		significant differences in incidence. The impact of ADA on PK, efficacy and safety should be assessed. Proposed change: 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. Equivalent immunogenicity assessment should include detection of ADAs, but there should be special focus on neutralizing Abs, antibodies that affect PK, and safety-related findings. Prelicensing safety data should be….	Not accepted. This information is specifically described in the guideline on immunogenicity of monoclonal antibodies.
393	2	Comment: The sentence is repetitive and not really necessary, since this is required in all situations. Proposed change (if any): Delete the sentence.	Not accepted. This sentence is included for clarification.
394 - 396	3	Comment: Is there a minimum number of subjects or a duration of exposure that is required? Proposed change (if any): please specify if there is a minimum number of subjects or a duration of exposure that is required.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
394-398	22	**Comment:** We suggest this section specifically state that sample size estimates for the program should take the demonstration of safety profile and immunogenicity into account. Ultimately, active surveillance post marketing could be required for sufficient exposures treated for a sufficient duration to be achieved, but pre-marketing, a certain level of confidence in the safety/immunogenicity profiles must be established by study of sufficient patients to avoid a "Type II error."	Accepted.
394-398	20	Comment: It should specifically state that sample size estimates and duration for the program should take the demonstration of safety profile and immunogenicity into account. Ultimately, active surveillance post marketing could be required for sufficient exposures treated for a sufficient duration to be achieved, but pre-marketing, a certain level of confidence in the safety/immunogenicity profiles must be established by study of sufficient patients to avoid a "Type II error".	Accepted.
395	17	Comment: "Pre-licensing safety data should be obtained **in a number of patients sufficient to determine the adverse effect profiles** of the biosimilar medicinal product." This would need more specification on what is the sufficient number of patients. And would this mean the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		need for a pre-license safety (e.g. open-label) study? A clarification of this issue is kindly requested.	
396	21	**Comment:** Please indicate the comparative nature of the exercise **Proposed change (if any):** "medicinal product in a comparative manner to the reference mAbs. Care should be...	Accepted.
396	20	Comment: Please indicate the comparative nature of the exercise Proposed change: "medicinal product in a comparative manner to the reference mAbs. Care should be..."	Accepted.
397-398	21	**Comment:** advice to focus (only) on adverse reactions described for the reference product seems too restrictive. **Proposed change (if any):** Modify to: "Particular attention should be paid to the adverse reactions described for the reference product"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Clarifying additions: adverse reactions and immunogenicity described for the reference product. Study duration has to reflect pharmacokinetic and pharmacodynamic aspects of duration of exposure respectively effect duration and for products intended to be used in multiple dose settings, multiple dose safety data are required.	
397 – 398	3	Comment: Advice to focus (just) on adverse reactions described for the reference product seems too restrictive. Proposed change (if any): "Particular attention should be paid to the adverse reactions described for the reference product."	Accepted.
399-404	21	**Comment:** It would be useful to emphasise the importance of identifying the biological product in adverse effect reporting. Potential rare events as occurred with the originator product during use in the market need to be addressed also pre-clinically in order to gauge the risk for the biosimilar and minimize the risk for patients. Please see also the clarifying comment below.	Accepted. However, this is already included in the Pharmacovigilance section of the guideline and will therefore not be included in this section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): ... similar pharmacovigilance activities, reporting obligations and risk minimisation measures as those of the reference	
399 - 400, 447 - 465	5	Comment: The clinical safety section of the draft guideline notes that rare events are not likely to be detected in a biosimilar's preauthorization program and that, consequently, a biosimilar applicant must propose pharmacovigilance and risk management activities for the postauthorization period. We suggest the guideline also note additional reasons for pharmacovigilance, which include: monitoring for potential clinical impact of product drift and monitoring for quality problems that give rise to a change in adverse event profile. Proposed change (if any): Guideline § 7 should include a general discussion of the purposes of pharmacovigilance, including the need to detect rare adverse events but also the need to monitor product drift and detect quality problems.	Partly accepted. All biologicals, including biosimilars, have the same Pharmacovigilance requirements. Collection of spontaneously reported ADRs is a requirement and should not be specifically described in this guideline. Regarding rare ADRs for which the reference product has additional requirements, e.g. registries, a statement is included in the guideline that participation in already existing registries is recommended. The quality of the biosimilar mAb is extensively assessed pre-licensing. Monitoring for product drift and quality problems is not specific for biosimilar mAbs but can also occur as a result of changes in the manufacturing process of the reference product. Including such a statement is this guideline is therefore outside the scope.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
399-402 447-465	20	Comment: In the draft guideline, the inability of applicants to detect rare adverse events in a preauthorization setting is posited as the justification for requiring pharmacovigilance and risk management plans. Post-approval biosimilars must complete requisite risk management plans. Each product should be considered a 'stand-alone' product (originator and biosimilar) after approval. Other potential issues are also addressed by pharmacovigilance, including the need to identify quality issues that may arise post authorization. The draft guideline should explicitly acknowledge these other bases for pharmacovigilance and risk management plans in § 7.	Partly accepted. Please refer to other comments related to this section.
399-404	20	Comment: It would be useful to emphasise the importance of identifying the biological product in adverse effect reporting. Potential rare events as occurred with the originator product during use in the market need to be addressed also pre-clinically in order to gauge the risk for the biosimilar and minimize the risk for patients. Proposed change: "... similar pharmacovigilance activities, reporting obligations and risk minimisation measures as those of the reference	Partly accepted. The need for risk minimisation activities has been included in section 7. Regarding the potential rare events, these should be discussed in the RMP and the need for additional activities should be described.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: Require more active methods since they are necessary to ascertain with reasonable confidence that incidence rates for such rare events are not more frequent when product attributes, including formulation, are considered. Additionally, the identification of such events may not be feasible if these are now multisourced as patients would be switching as well so there would be potential confusion as to which manufacturer's product they are receiving. Therefore, require clearly unique naming identification as well as clear tracking of switching to determine which product has the findings.	The issue of traceability is described in the new Pharmacoviglance legislation (Directive 2010/84/EC). With regard to causality assessment in the case of switching this is very challenging from a Pharmacovigilance perspective. However, the issue of switching is dealt with at a national level. In addition, adverse reactions based on the pharmacology of the biosimilar are not expected to be product specific.
401	10	Proposed change (if any): Insert: "which should be no less rigorous than those which are required for the reference product" at the end of sentence in line 401. Proposed change (if any): Delete the word "usually".	Not accepted. In general, this will be the case. However, there can be situations in which there are different requirements.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
402	10	Comment: In certain circumstances not only does immunogenicity alter the efficacy parameter it should be further considered in the individual benefit/risk equation. Proposed change (if any): Insert " and potentially altered benefit/risk balance"	This comment is unclear. No change necessary, since the benefit/risk balance is outside the scope of this guideline (the guideline should not pre-empt any decision of the CHMP).
402-404	22	**Comment:** The Guidance states, "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." We suggest that if rare events have been identified for a monoclonal antibody, that active monitoring be recommended for that event to confirm similar incidence to the originator. We also suggest EMA require more active methods since they are necessary to ascertain with reasonable confidence that incidence rates for such rare events are not more frequent when product attributes, including formulation, are considered. (Passive identification may not be feasible if product are multisourced without unique identification.)	Not accepted. It is unfeasible and unnecessary for the biosimilar mAbs to perform additional post-marketing studies for all rare ADRs identified for the reference product. This is far beyond the scope of showing biosimilarity. If the reference product has additional Pharmacovigilance requirements, e.g. in relation to Progressive multifocal leukoencephalopathy (PML), this should also be applied to the biosimilar mAb as already included in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: We suggest the additional language, "**To ensure that the risks of rare events could be accurately evaluated post-approval, the risk management plan should require active monitoring for those events, and should also include unique naming and labelling measures to ensure that there is clear tracking of the rare events to the manufacturer.**"	
405 - 410	5	Comment: The clinical safety section of the draft guideline states that with respect to oncology indications that require several treatment cycles, "[i]t may be advisable to extend the clinical study as a post-authorisation follow-up study to a full treatment cycle, where relevant and feasible." This seems to imply that the CHMP would permit a clinical safety trial to be shorter than a full treatment cycle. The guideline should instead require safety data from the entirety of treatment of the patient with the product (multiple full cycles, where necessary). In rare situations where the EMA accepts data from one full treatment cycle alone, which must be scientifically justified, any patient who received the biosimilar for one cycle should be permitted (for safety reasons) to continue using the biosimilar throughout his multi-cycle regimen. Safety data from these subsequent cycles should, even if not required for authorization, be collected, analyzed, and submitted to the EMA. Proposed change (if any):	Partly accepted. Depending on the end-point used in the clinical efficacy part of the trial, clinical efficacy can in some cases be shown without completion of the full treatment cycle. In such a case collection of safety data might be required during marketing. The last sentence of this part of the guideline has been slightly amended to support the collection of safety data in the post-marketing setting.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The CHMP should remove the sentence on lines 408-410 and should amend the clinical safety section of the guideline to recognize the issues discussed above.	
405-410	20	*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.* Comment: Lines 405-410 could be interpreted to permit a biosimilar applicant to receive approval based on an oncology clinical safety study that did not include a full treatment cycle. Safety data should be gathered from a trial that encompasses the entirety of treatment of the patient (a full course of treatment). Comment: The CHMP should clarify terminology. Cycle of treatment (for example 7 days followed by 21 days off treatment) vs. 5 cycles that would make up a treatment course. We believe that the comment relates to showing similarity without a full course of treatment (1 or 2 treatment cycles). In this case continuing the trial	Please refer to the previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		until all cycles are completed would be required given that anything less would constitute inadequate treatment for the patients.	
409-410	21	**Comment:** Not clear, why the full treatment cycle would be generally requested as follow-up study only? Please explain. **Proposed change (if any):**	Please see previous comment.
410	22	**Comment:** The causes of immunogenicity are not fully understood. There are multiple risk factors including aggregation, oxidation, reduction, adjuvant effects, and improper folding which could impact the immunogenicity of a protein therapeutic. Because not all of the risk factors are fully understood, and the degree to which these multiple risk factors contribute to overall immunogenicity are also not well understood, it cannot be assumed that different manufacturers of a therapeutic protein will produce products with identical immunogenicity. Antibodies against a therapeutic protein can reduce the level of circulating drug to a degree that can limit the drug's efficacy. It is important for physicians to understand the immunogenicity of similar mAbs so they can make an informed decision on which version is best for their patient. Only through properly powered clinical trials	Party accepted. Immunogenicity data is important for biosimilar mAbs and reference mAbs. In most cases it is not necessary to collect 12 months of immunogenicity data before approval but it is acceptable to have a follow-up after approval. A statement is included in the guideline underlining the need to discuss the need for additional immunogenicity data in the RMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		lasting at least 12 months can the immunogenicity of a mAb be determined. **Proposed Change:** We recommend that the EMA maintain the requirement for a pre-authorisation evaluation of immunogenicity including at least 12 months follow-up data, unless otherwise justified by the limited duration of therapy.	
411-419	21	**Comment:** Immunogenicity should always be assessed for biosimilars because factors that influence immunogenicity are incompletely understood and analytical techniques alone cannot assess the risks to the patients. It is additionally possible that Abs against a biosimilar will cross-react with other products, potentially rendering those therapeutically unusable by the patient. It should be clearly written in the guideline that robust comparative pre-authorisation immunogenicity data in relevant indications should be always provided. Provided the study is regarded safe only in naive patients, the approved indication should also be naive patients only? **Proposed change (if any):** Modify guidance. Immunogenicity should always be assessed for every	Not accepted. Collection of immunogenicity data in all indications is beyond the scope of showing biosimilarity and should be assessed on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		indication.	
411-419	7	Comment: The causes of immunogenicity are not fully understood. There are multiple risk factors including aggregation, oxidation, reduction, adjuvant effects, and improper folding that could impact the immunogenicity of a therapeutic protein. Therefore, it cannot be assumed that different manufacturers of a therapeutic protein will produce products with identical immunogenicity. Antibodies against a therapeutic protein can reduce the level of circulating drug to a degree that can limit the drug's efficacy. It is important for physicians to understand the immunogenicity of biosimilar mAbs in the context of individual patient history in order to make an informed decision on which product is best for their patient. It is recommended that immunogenicity data in each indication (indication-specific) are requested since the sensitivities of the different populations could easily differ as a consequence of the biosimilar product's attributes.	Not accepted. Please see previous comment.
411-419	20	Comment: The causes of immunogenicity are not fully understood. There are multiple risk factors including aggregation,	Not accepted. Please see previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		oxidation, reduction, adjuvant effects, and improper folding which could impact the immunogenicity of a protein therapeutic. Because not all of the risk factors are fully understood, and the degree to which these multiple risk factors contribute to overall immunogenicity is also not well understood, it cannot be assumed that different manufacturers of a therapeutic protein will produce products with identical immunogenicity. Antibodies against a therapeutic protein can reduce the level of circulating drug to a degree that can limit the drug's efficacy. It is important for physicians to understand the immunogenicity of similar mAbs so they can make an informed decision on which version is best for their patient. It is additionally possible that Abs against a biosimilar and/or originator will cross-react with other products, potentially rendering those therapeutically unusable by the patient. It should be clearly written in the guideline that robust comparative pre-authorisation immunogenicity data in relevant indications should be always provided. Proposed change: Do not allow exclusion, unless specifically justified, of such patients as "repeat" exposures from an innovator to biosimilar, or vice versa, could be the rule in practice and, if order of treatment affects tolerability/antigenicity to any degree, it is better that this be known up front rather than using exposures in	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		an uncontrolled setting for such assessments. Also modify to indicate that normally immunogenicity should be assessed for every indication.	
413-415	22	**Comment:** The Guidance states, "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." We suggest that EMA not allow exclusion of such patients as "repeat" exposures from an innovator to biosimilar, or vice versa, could be the rule in practice and, if order of treatment affects tolerability/antigenicity to any degree, it is better that this be known up front rather than using exposures in an uncontrolled setting for such assessments. **Proposed Change:** We suggest deleting this sentence or modify to suggest that immunogenicity studies should include both patients naïve to reference mAb as well as those switched from reference mAb to reflect actual conditions of use once the biosimilar is approved.	Partly accepted. It is agreed that information on immunogenicity after switching is important. However, for the biosimilarity exercise it is aimed to show a similar safety profile between biosimilar and reference product. Therefore, patients treated should be as comparable as possible and this can best be achieved for naive patients. The need for additional information on immunogenicity after switching might be described in the RMP of the biosimilar mAb..
413-415	15	Comment: Reference is made to the statement, "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	Please refer to previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		decrease sensitivity for detecting differences." Whether adverse events related to immunogenic reactions to the biosimilar medicinal product will have to be separately assessed in treatment naïve patients and non-naïve patients should be assessed by the applicant. Patients who were pre-treated with the reference product may reveal cross-reactivity with the biosimilar medicinal product. Given this, the value of analysis of immunogenicity in pre-treated versus naïve patients will need to be considered on a case-by-case basis (i.e., based on clinical relevance). Proposed change: Please clarify in final guidance.	
413-420	10	Comment: Suggest strengthening the wording regarding switching patients from the reference product to the biosimilar in the clinical development assessment. Proposed change (if any): "safety data should ideally be gathered on the biosimilar product in development in patients naïve to the reference product" Proposed change (if any): Change "might" to "will"	Not accepted. The proposed change will not change the meaning of this statement.
415-418	17	Comment: The term "study" misleadingly suggests the need for a	Accepted.

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		separate study on immunogenicity. To express more clearly that immunogenicity can also be integral part of other studies the more open term "investigation" is suggested. Proposed change: "~~Study~~ **Investigation** 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."	
415-419	20	Comment: The draft guideline would permit applicants to develop their biosimilar mAb in a different cell expression system from that used by the reference product sponsor, including cell expression systems for which there are limited experience in humans. Different host cell systems can lead to different post-translational modifications and impurity profiles, among other things, and these differences can affect the immunogenicity and other clinical outcomes of the biosimilar mAb.	Use of a different cell expression system by the biosimilar mAb might be accepted and it is acknowledged that this can alter the immunogenic potential. However, based on the quality characterisation and the pre- and clinical studies, sufficient data on comparability with the reference mAb should have been generated at the time of MAA
416	4	Comment: There is no evidence of increased risk of immunogenicity by using a different host cell Proposed change (if any): Delete	Not accepted. A different host cell can, for example alter the glycosylation pattern which might result in a different immunogenicity. This has been clarified in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
420	21	**Comment:** It is important that biological products be clearly identified and distinguished from other products in the post-marketing space. It would be useful to stress that identification of products is necessary for traceability/ pharmacovigilance purposes. **Proposed change (if any):**	Accepted. A statement is included in section 7 of the guideline and the stakeholder is referred to the Pharmacovigilance legislation (Directive 2010/84/EC).
420	11	Comment: "long term immunogenicity and safety post authorization" - the originators may not need to assess immunogenicity in the post-market environment. However, this might be very reasonable for the biosimilars, and if so, should be specified, unless it can be shown that collection of immunogenicity post-approval would not add importantly to safety knowledge. For instance, etanercept has very low levels of neutralizing antibodies and the value of collecting this post- authorization would be questioned. But for other MABs, it could be important. Proposed change (if any): It should be clarified if the ability to perform	Not accepted. The proposed change will not change the meaning of the guideline and is therefore not included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		immunogenicity testing in the post-approval environment is an expectation, unless if can be shown to not be of important value. In case of the same expression system, low immunogenicity observed with the originator, and low immunogenicity demonstrated in a reasonably sized clinical program, a long-term immunogenicity follow-up for a biosimilar product may not be required.	
420-421	20	Comment: Longer-term immunogenicity data (6-12 months) for an oncology indication should be required pre-authorisation - because differences in immunogenicity where the biosimilar has higher immunogenicity would have safety implications	Not accepted. This should be assessed on a case-by-case basis.
420 - 423	5	Comment: The clinical safety section of the draft guideline states that additional long-term immunogenicity and safety data "may" be needed postauthorization. It adds that "a post-authorisation concept for obtaining further indication-specific safety data may be needed." We recommend that the guideline more clearly differentiate between pharmacovigilance and postauthorization	Partly accepted. The wording in the draft guideline has been changed to take the comments of the stakeholder into account. However, some issues should be dealt with on a case-by-case basis and should therefore not be mentioned in this guideline as a requirement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		studies. Postauthorization safety data and data pertinent to adverse clinical sequelae of immunogenicity, gathered through pharmacovigilance, are always necessary — for example, to detect rare adverse events, to monitor product drift, and to detect quality problems. Longer term postauthorization studies may be needed for any of a number of reasons, including where an interim endpoint has been used for approval or where data from only one cycle of a multi-cycle oncology therapy were submitted. Also, in many cases it will be inappropriate to defer indication-specific safety data to the postmarket period. Wherever there is a reasonable possibility that safety differences between the products could emerge in an unstudied indication (e.g., because of different concomitant medications, different doses, different susceptibility of the population to adverse events, etc.), the safety of the indication should be assessed prior to market authorization. Proposed change (if any): ~~"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.~~ **Additional long-term immunogenicity and safety data will be required**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		post-authorisation. A risk management program and pharmacovigilance plan must be submitted in accordance with current EU legislation and guidelines. In addition, postauthorization studies may be necessary for a variety of reasons (for example, where the duration of the clinical safety and efficacy study is short), and safety data must in each of these cases be assessed and evaluated. If safety data are extrapolated across indications, postauthorization safety data must be gathered for each indication. Wherever there is a reasonable possibility that safety differences between the products could emerge in an unstudied indication (e.g., because of different concomitant medications, different doses, different susceptibility of the population to adverse events, etc.), however, the safety of the indication should be assessed prior to market authorization as well."	
420-423	17	Comment: Provided that high similarity of physicochemical and biological properties is demonstrated already it is not to be expected that the safety profile of the biosimilar and reference mAb will be different. Nevertheless, sufficient safety data prior to licensure should always be provided to ensure that the biosimilar has no unexpected safety issues. To have it confirmed for the most frequent and common side effects prior to licensure and the necessity of post-approval studies for the less frequent	This is already included in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and less common side effects need to be further evaluated on a case-by-case basis. In addition, to establish comparable immunogenicity data based on the applicability of the risk based approach, shorter term immunogenicity data in the most sensitive patient population would be sufficient for marketing authorization applications while longer term data would need to be provided post-approval.	
421-423	22	**Comment:** The Guidance states, "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." This requirement needs to be strengthened as the sensitivities of the different populations to immunogenic effects and other adverse consequences of treatment could easily differ as a consequence of the biosimilar product's attributes. Recent severe clinical adverse reactions (dramatic increase in rates of pure red cell aplasia due to erythropoietin source and container/closure leachate changes) should provide adequate cautionary evidence for extrapolating immunogenic properties. Another example is infliximab, well known to have a widely variable immunogenicity rate, ranging from less than 5% to 35%. Moreover, differences in indications for the reference product's patient populations differ between indications in disease progression, immunocompetence, dose, age, and/or concomitant therapies. All of these factors are known to affect immunogenological	Not accepted. Including the proposed change by the stakeholder will not give any opportunity **not** to conduct a long term immunogenicity study in each indication. This should be assessed on a case-by-case basis and the wording will therefore not be changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		prosperities. Small changes in biochemistry of the mAb could influence and change the mAb's immunogenicity in ways that should be studied in each clinical indication, as studying only one patient population may not represent the immune reactions in a more immunocompetent population, etc. **Proposed Change:** We propose to revise "~~may be needed~~" to "**<u>should be obtained</u>**".	
421-423	20	Comment: The sensitivities of the different populations to immunogenic effects and other adverse consequences of treatment could easily differ as a consequence of the biosimilar product's attributes. The requirement for post-authorization safety data should be strengthened in the following sentence: "*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*." Proposed change: "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~~ **<u>should be obtained</u>**".	Please see previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
424	10	Comment: This section proposes that extrapolation of indication be based on the sensitivity and degree of similarity achieved during clinical development. This is a reason to ensure that the clinical development to establish similarity in terms of efficacy and safety is robust enough. However, extrapolation of indication will not be necessarily possible as the efficacy and safety of a biosimilar mAb may vary in comparison to the reference product for the different indications of the reference mAb. The innovator company is required to design and execute clinical trials for each indication. Commercial promotion by innovator companies of off label use is strictly prohibited by the EMA and health care authorities. Biosimilar companies should also have to demonstrate efficacy and safety in each indication and biosimilar companies shall only be allowed to promote additional indications after successful clinical trials and approval by the EMA. Proposed change (if any): Extrapolation of indication is not allowed	Not accepted. A biosimilar development programme establishes biosimilarity, not efficacy or safety per se as an innovator company does for a novel mAb. Therefore, extrapolation is possible for biosimilars based on the overall scientific evidence provided. This has also been accepted for other biosimilars before.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
424 - 445	5	Comment: Section 6 of the draft guideline discusses the extrapolation of PD data. We agree with the observation that separate data for each indication may be needed 1) where pivotal evidence is based on PD and the indications have different mechanisms of action (lines 428-430) and 2) in many cases where the mAb is both an immunomodulator and anticancer antibody (lines 433 and following). The guideline should also discuss several other factors that may limit the ability of applicants to extrapolate data across indications, even within the same therapeutic area. These include: • whether the indications use monotherapy or require combination therapy, • differences in concomitant medications (these may reveal or mask certain adverse event differences), • differences in immune status of the patients (immunogenicity differences may not be manifest in immunocompromised patients or may be more apparent in children or younger patients), • differences in the site of action of the mAb (biodistribution may differ), • differences in route of administration (bioavailability may differ), • differences in dose (differences may manifest only at higher or lower doses), and	Not accepted. The points put forward may in some cases be problematic, but not in others, and if the guideline made a particular prohibition of extrapolation based on these points, then extrapolation would be virtually impossible. "Adequate justification" is included (lines 427-428 in the draft guideline document), and this covers the points made implicitly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• whether the activity of the antibody in the indications depends on different parts of the molecule (this factor is already addressed in the discussion regarding antibody-dependent cell-mediated cytotoxicity versus signaling inhibition). Proposed change (if any): The discussion of extrapolation of indications should indicate that this extrapolation, whether with respect to safety or efficacy or both, should be based on compelling science-based arguments. As described above, the guideline should be explicit regarding the many factors that could lead to the emergence of differences in clinical effects in one indication but not another (beyond just mechanism of action and therapeutic area), and it should note that the applicant must address all such potential differences.	
424-445	14	Comment: We support the concept of extrapolation as provided in the guideline in case (1) the indications share the same mode-of-action; (2) the analytical characterization and other data show high biosimilarity and (3) a clinical study is conducted in an indication sensitive to show potential differences between reference and biosimilar product. We consider justifiable, science- and data-based extrapolation as equally essential for biosimilar development as for originator biopharmaceuticals upon	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		manufacturing changes (Nature Biotechnology 29, 310-313, 2011). In both cases, a similar scientific approach demonstrating "comparability" leads to extrapolation across multiple indications. Proposed change: No changes are recommended	
424-445	20	Comment: Draft guideline section 6 discusses the extrapolation of PD findings. We agree with the observation that separate data for each indication may be needed 1) where pivotal evidence is based on validated PD markers and the indications have different mechanisms of action (lines 428-430) and 2) where the mAb is both an immunomodulator and anticancer antibody (lines 433 and following). The guideline should also discuss several other issues that may limit the ability to extrapolate data across indications. These include: (1) whether the indications use monotherapy or require combination therapy, (2) differences in concomitant medications used with the mAb (as medications may reveal or mask certain adverse event differences), (3) different immune status of the patients (as immunogenicity differences may not be manifest in immunocompromised patients or may be more evident in younger patients), (4) differences in the site of action of the mAb (as biodistribution may differ), (5)	Please refer to similar comment from stakeholder 5. As regards the extrapolation from "palliative" to "potentially curative" settings, this is an important but not sufficient criterion to prohibit or allow extrapolation. Again, it will depend on the strength of the overall database demonstrating biosimilarity, and the scientific justification. This scenario is covered in the text as it stands.

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		differences in route of administration (as bioavailability may differ), (6) differences in dose (as differences may manifest only at higher or lower doses), and (7) whether the activity of the antibody in the indications depends on different parts of the molecule. (We note that this last factor is already addressed in the discussion regarding ADCC versus signalling inhibition.) For indications where cure is the achieved treatment outcome of the reference product and there remains uncertainty regarding the mode of action, extrapolation across indications should not be permitted based on PD findings, and clinical similarity should be established in those indications with appropriately powered equivalence clinical trials in order to mitigate any risk to patients. Proposed change: The discussion of extrapolation of indications should indicate that such extrapolation, whether of safety or efficacy, should be supported by compelling science-based arguments. As described above, the guideline should be explicit regarding the many factors that can differ between indications (beyond just mechanism of action and therapeutic area) and that could lead to emergence of differences in clinical effects in one indication but not another. The guideline should also state that the sponsor must address such potential differences. Extrapolation to curative settings may be a bigger risk to patients than palliative / metastatic settings. In contrast to metastatic disease, curative	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		settings such as adjuvant breast cancer or diffuse large B cell lymphoma should have equivalence margins that are tighter in order to ensure more precision around the estimate of the treatment effect.	
425-427	20	Comment: The wording "is possible" is too absolute; "may be possible" is more realistic. Proposed change: Please reword. "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~~ **may be** possible..."	The sentence needs to be read as a whole: "is" possible "based on overall evidence". This implies that if the overall evidence is not sufficient, extrapolation will likely be questioned.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
425 - 428	6	Comment: • The guidance should reiterate the criteria for extrapolation outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues". It should also emphasize that possible safety issues in different subpopulations should be evaluated in clinical trials. • For those biopharmaceuticals where the mechanism of action is comprehensively understood, extrapolation may be feasible on the basis outlined in the above mentioned general guidance. However, for mAbs, where the mechanism of action is rather complex and often only partially understood, a more cautious approach regarding extrapolation should be taken. • Example autoimmune diseases: In spite of sharing some common pathogenetic mechanisms, different autoimmune diseases can vary significantly in e.g. target organ(s), clinical manifestations, time of onset, prognosis, speed of progression, gender prevalence, etc. As a result, response to immunomodulators even with identical mechanism of action and PD is extremely variable. • Extrapolation of safety also poses risks because the safety profile of immunomodulators across the different diseases can vary even within the same	Not accepted. No need to re-iterate content if it is appearing in another guideline that is relevant and part of the references. Not accepted, since the database and the scientific justification are important aspects. It is unclear with what rationale extrapolation would not be possible if a mechanism of action would be complex (no rationale given). Example acknowledged. However, this is not related toestablishing biosimilarity, rather establishing efficacy per se. Please see comment above.

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		molecule. • In general, extrapolation of indications requires well-balanced assessments and might not be possible in many cases. To mitigate risks associated with extrapolation of indications, similarity should be demonstrated in the indication where the treatment with reference product provides the best outcome (e.g. OS). • If similarity is established in the appropriate indication, extrapolation to other indications may be granted in case of proper justification (e.g. high degree of molecular similarity, same expression system, same mode of action, same drivers of PK, validated in vivo PD surrogates, etc.).	Partly agreed. This is why the most sensitive model is proposed in the guideline. Therefore, the guideline already covers this aspect. Partly agreed, this is however covered (lines 427-428 of draft guideline text).
425-428	20	Comment: "*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*." Guidelines on mAb and immunogenicity should be consistent. The recent immunogenicity guideline is stronger on this position and states, "Every therapeutic mAb needs to be evaluated for immunogenicity individually and all immunogenicity strategies should be adapted for each mAb development programme." The	Not accepted, since the guideline on immunogenicity assessment of mAbs concerns all mAbs, including new-in-class mAbs. For the latter, the statement is correct that immunogenicity cannot be extrapolated. This may likewise be true for biosimilar mAbs, but one cannot make a general statement that extrapolation is not possible in any circumstance. At the present time, this must be left to the individual data as a case-by-case decision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		two guidelines should be aligned. Proposed change: Add: "**<u>Immunogenicity cannot be extrapolated to other indications where patient populations may exhibit differences in immune competency, co-morbidities, etc. For example, the immunogenicity observed when a biologic is administered to an immunosuppressed population (e.g. when rituximab is given to cancer patients) cannot be extrapolated to the situation where the same biological product is administered to patients with rheumatoid arthritis. The patients in the latter category would be far more likely to mount a severe immune response to the biological product.</u>**"	
425-432	22	**Comment:** The Guidance states, "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 immunomodulatory and as an anticancer (cytotoxic)	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging." If "uncertainty exists," as suggested by both of these excerpts, then extrapolation should not be allowed. We suggest that this could be clarified **Proposed Change:** We suggest the additional language, **"Comparative PD studies may be sufficient to extrapolate to the reference product's efficacy profile when the following are true:** 1. **The mechanism of action of the biological product is shared in the intended condition(s) of use;** 2. **The proposed biosimilar has been shown to have equivalent PK and PD profiles to the reference product in the same route of admistration intended in all indiactions** **Clinical studies in the most senstitive indication have been conducted and demonstrate equivalent safety and efficacy. If PD supports such a showing, PD markers must have a well-established relationship with the efficacy of the biologic and are validated and approved by regulatory authorities as an endpoint to support**	BMWP considers that the current text is already cautious enough. Putting this proposal to the guideline may be too restrictive, and more experience has yet to be gained. At the present stage, it is important to stress that justification and the overall dataset is key.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		registration in the intended condition of use; and even when the relationship between dose-exposure and the surrogate marker is well known, is sufficiently characterized, and can be extrapolated to different populations, clinical safety and immunogenicity studies should not be waived."	
427-428	11	Comment: Line 427-428 states that extrapolation of clinical efficacy and safety to other indications is possible based on the evidence provided and with adequate justification. It's not clear from the Guideline what that justification would normally entail and whether the agency has an opinion on how to select the "reference indication" from which the other indications will be extrapolated. The Guidance needs to provide more details regarding criteria of selecting a "reference indication".	While it would in principle be desirable to be more specific, the guideline is intended to introduct general principles. The justification to be provided may include data generated by the Applicants themselves, but also experimental data from literature and other sources. It will thus depend on the individual scenario what justification will be accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
428	20	Comment: Comparative PD studies may be sufficient to extrapolate to the reference product's efficacy profile when the following are true: • There is sufficient knowledge of the PK/PD profile of the reference product, including the dose-response; • The mechanism of action of the biological product is shared in the intended condition of use; • The PD markers have a well-established relationship with the efficacy of the biologic and are validated and approved by regulatory authorities as an endpoint to support registration in the intended condition of use; and • The proposed biosimilar has been shown to have equivalent PK and PD profiles to the reference product. Even when the relationship between dose-exposure and the surrogate marker is well known, is sufficiently characterized, and can be extrapolated to different populations, clinical safety and immunogenicity studies should not be waived.	This is a repetetive comment (please see above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
428-430	21	**Comment:** "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." If a validated surrogate PD endpoint is available (eg: BP drop, HbA1c), then they provide confidence related to outcome. In such cases, similarity can be assessed based on that PD endpoint. A PD marker is clinically relevant to one indication does not necessarily mean there are clinically relevant PD markers for other indications for which the reference mAb has been proved. And again, using PD data as pivotal evidence of biosimilarity should be justified on a case-by-case basis, and comparative human safety data are needed on all indications. **Proposed change (if any):** If pivotal evidence for biosimilarity is based on human 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. The choice of the PD marker(s) for the additional indications should be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		justified.	
428-430 and 435-436	22	**Comment:** The section on extrapolation of indications applies the correct principle to ensure that data is generated for each separate mechanism of action for a product, however, the section is not precise. We suggest that additional clarity be provided regarding the expectations especially where the mechanism of action is unclear. It should be unambiguous that if comparative clinical data are required to establish biosimilar efficacy via a given mechanism of action, then this should be true for all mechanisms of action. However, the text is vague on whether clinical data (PD or outcome) or non-clinical PD data would suffice. In particular, the text on 435-436 implies that quality and non-clinical data can suffice for extrapolation between two radically different MOAs (cytotoxic vs. immune modulator). This appears to contradict previous guidance which requires clinical evidence of biosimilarity using either a relevant PD marker or a	Partly accepted. BMWP agrees that the text suggested that quality and non-clinical data are the mainstay for extrapolation, which is not correct. These two disciplines rather form the basis on which the ultimate argumentation with clinical data rests. This has therefore been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical outcome measure for a given mechanism of action. **Proposed Change:** (428-430) We suggest the additional language**, "**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 **clinical** data to cover pharmacodynamics for all claimed clinical indications." **Proposed Change:** (435-436) We suggest the alternative text, **"**The basis for such extrapolation **should, at a minimum, include evidence that the same mechanisms of action are relevant to both the clinically evaluated indications and the proposed extrapolated indications. Further, because some mechanisms of action, e.g ADCC, could be more relevant in certain indications, the rationale for extrapolation should be supported by** an extensive quality and non-clinical database, including potency assay(s) and in-vitro assays that cover the functionality of the molecule."	This addition would shift the meaning of the paragraph, since it is not necessarily clinical data, but could also be PD data. This proposal is problematic, since this paragraph relates to those mAbs which have both an indication as immunomodulator and as anticancer therapeutic. In some scenarios it may not be clear to what extent the mechanism of action is the same. Therefore, the draft guideline discusses this scenario further to highlight uncertainties and how to potentially meet them. It seems that the message suggested here is, otherwise, covered in the current text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
429	17	Comment: No additional clinical data are needed for extrapolation. Proposed change: replace: ".., then applicants should provide relevant data to cover …" by: "…, then applicants should provide relevant **in vitro or in vivo d**ata to cover…"	Not accepted, since the guideline should leave any possibility open, depending on the scenario. It will be up to the Applicant to convincingly establish biosimilarity with the datapackage provided. This may or may not be without additional clinical data.
433-437	7	Comment: It should be clarified that immunogenicity profiles cannot be extrapolated across indications where either patient population or concomitant medications may affect the immune response. Whilst this section suggests that extrapolation is challenging where multiple mechanisms of action or indications exist, the circumstances whereby extrapolation may be possible should be clarified. These circumstances may include where comparative PD studies exist and: • there is sufficient knowledge of the PK/PD profile of the reference product, including the dose-response; • the mechanism of action of the reference product is understood in the intended condition of use; • the PD markers have a well-established relationship	Please see similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with the efficacy of the reference product in the intended condition of use; and • the proposed biosimilar has been shown to have equivalent PK and PD profiles to the reference product. It is important that clinical safety and immunogenicity studies are not waived, even when the relationship between dose-exposure and the surrogate marker is well known and sufficiently characterized, and can be extrapolated to different populations.	
433-445	21	**Comment:** This paragraph may be interpreted that very limited animal and human data are needed on biosimilar mAbs. We disagree that use of only quality/ preclinical data would be adequate. In our opinion there may be risks in extrapolation of data if the originator product is used in different diseases, with different doses and/ or different combinations in life threatening diseases. Clinical study or studies to assess the nature and	This has been clarified, please see above. Quality and non-clinical data are the basis on which the further concept rests. As regards the other points, please refer to comments made elsewhere in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		impact of actual or potential structural differences between the biosimilar product and the reference product instead of extrapolating from one indication to another are needed. This is especially necessary with regards to the adjuvant setting or acute versus chronic applications. This is also relevant when different dosing regimens or different standard chemotherapy combination partners are used in different indications or lines of therapy: e.g. 500 mg/m2 dosing in CLL vs 375mg/m2 in NHL, CHOP in combination with Rituximab in DLBCL vs FC in combination with Rituximab in CLL vs Bendamustin in combination with Rituximab in FL. **Proposed change (if any):** Please state clearly that normally robust, comparative clinical safety and efficacy data are needed on biosimilar mAbs. We recommend that mAb specific non-clinical and clinical guidelines are drafted to provide clear, transparent guidance to stakeholders	
436-437	22	**Comment:** Guidelines on mAb and immunogenicity should be consistent. The recent immunogenicity guideline is stronger on this position and states, "Every therapeutic mAb needs to be evaluated for immunogenicity individually and all immunogenicity strategies should be adapted for each mAb development programme." The two guidelines should be aligned.	Please see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: We suggest EMA add, "**Immunogenicity cannot be extrapolated to other indications where patient populations may exhibit differences in immune competency, co-morbidities, etc. For example, the immunogenicity observed when a biologic is administered to an immunosuppressed population (*e.g.*, when rituximab is given to cancer patients) cannot be extrapolated to the situation where the same biological product is administered to patients with rheumatoid arthritis. The patients in the latter category would be far more likely to mount a severe immune response to the biological product.**"	
433-445	20	Comment: The guideline appears to imply that quality and non-clinical data may provide sufficient justification for extrapolation from a given clinical indication (studied in comparative clinical studies), to additional indication with a different reliance on mechanism(s) of action. While the intent of this text is to cover a narrow class of therapeutics with multiple mechanisms of action (immunomodulators that are also cytotoxic agents), the text could be clarified to explain that this does not contradict the preceding text (lines 425-432) with regards to the necessity for a common mechanism of	Please see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		action in the extrapolated indications. Proposed change: "The basis for such extrapolation **should, at a minimum, include evidence that the same mechanisms of action are relevant to both the clinically evaluated indications and the proposed extrapolated indications. Further, because some mechanisms of action, e.g. ADCC, could be more relevant in certain indications, the rationale for extrapolation should be supported by** an extensive quality and non-clinical database, including potency assay(s) and in-vitro assays that cover the functionality of the molecule."	
437	21	**Comment:** In fact the impact of different disease states, immune status, and concomitant medications on the potential for an immunogenic response is currently not predictable and therefore obtaining empirical, comparative data are generally necessary for each indication. **Proposed change (if any):** Modify guidance to insist that comparative clinical immunogenicity data be usually obtained empirically from each patient population.	Please see above and revisions in the safety section of the guideline where immunogenicity across indications has been further mentioned.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
441-444	15	Comment: The reference to literature support "to identify what is know about the potential signalling inhibition by the reference mAb that would not be covered by ADCC/CDC test" is welcome.	Comment noted. BMWP suggests putting an "e.g.", since signalling inhibition may only be one of more scenarios which could be used to support extrapolation.
447	21	**Comment;** Suggestion to rename to "post-approval use of Biosimilars" with the following subheaders: *1. pharmacovigilance* Requirement for an RMP with additional focus on: - PV measures, comparable if not more stringent than the reference product - evaluation of immunogenicity in the post-marketing setting: how to identify immunogenicity risk including secondary loss of effect in naive patients, any loss of effect not in naive patients, evidence of antibodies (neutralising vs. non-neutralising). - rare but serious adverse events, including infections - strategy of 'normal' PV measures should be discussed as the safety profile of biologics is different compared to small molecules. *2. traceability & naming* - it is important in the post-approval phase to distinguish easily between the biosimilar product and the reference product so that it is clear which product a	Not accepted. The heading and sub-sections of this section should be in line with other EMA guidelines. Partly accepted. This specific guideline should not describe the general Pharmacvogilance requirements which are laid down in pharmacovigilance legislation and guidelines. Within the Pharmacovigilance guidelines it is included that biosimilars have to submit a RMP. A statement has been included in the guideline that the need for additional immunogenicity data should be evaluated in the RMP. This is included in the guideline. This is a general Pharmacovigilance requirement and not specific for biosimilar mAbs. The guideline will therefore not take this into account. Partly accepted. The importance of traceability and naming is stressed in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patient has received. Product naming is covered, but other means of improving traceability could be mentioned: unique INN name, recording the lot numbers, etc. *3. product information* Because biosimilars are not equivalent to the reference product and because unique efficacy and safety data will be available, the product information should include these data. PI should distinguish data sources (reference product, biosimilar, extrapolation, others). There should be cross-references to the originator's PI Warnings and Precautions and to long term safety data monitoring/ collection. Labeling should also clearly indicate which indications are based on extrapolation of data because physicians, pharmacists and patients should be aware of the clinical data supporting an indication and of the instances in which indications are based on extrapolation of data. *4. substitution* A paragraph on substitution and the risks associated with this practice (although not endorsed by the EMA and prohibited in many countries) could be beneficial as inappropriate substitution could potentially occur when prescribers do not understand the potential risks involved and when the distribution systems allow or encourage automatic substitution. Substitution should be viewed as a change in clinical management. Also, to ensure that an accurate, 'un-polluted' safety database	Not accepted. Product information and substitution are beyond the scope of this guideline and should therefore not be included in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would be established, substitution should be prohibited. More transparency is required as if substitution is not properly managed it will dilute safety database as well as hamper the pharmacovigilance activities.	
447	21	Comment: Since there is no unmet medical need if the reference product on the market, robust pre-approval data are necessary to ensure patient safety, and efficacy of the product. Conditional type approval based on post approval clinical data alone should not be acceptable. In addition, since the biosimilar mAbs may be approved only also for use in part of the indications/ routes of administration approved for the reference product, it will be highly relevant to define the measures to guaranteed that the biosimilar mAb is used in authorised indications only.	Biosimilar medicinal products are not expected to fulfil the legal requirements for a conditional MA in particular with regard to the unmet medical need. This is without prejudice to the possibility of requesting the conduct of studies as a condition of the marketing authorisation. There is indeed a potential for off-label use. However, off-label use should specifically be described in the RMP and PSURs as described in the GVP module and will therefore not be included in the guideline. It is not specific for mAbs, and therefore is rather a subject for the general biosimilar guidelines. Moreover, this issue will anyway be dealt with at the time of marketing authorisation application.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
447–465	14	Comment: Novartis does not concur with the proposed wording in the draft guideline since it seems that the proposed concept may have to "exceed routine pharmacovigilance requirements" for biosimilars. We request pharmacovigilance and risk management plans be the same for all biologics, including biosimilars. We suggest including a reference to the new EU pharmacovigilance framework that will require product name and batch number for adverse event reporting for all biologics. Proposed change: "The concept ~~may have to exceed routine pharmacovigilance, and may have to involve more standardized environments~~ should follow	The text has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacovigilance measures for biologicals according to the implementation of EU Pharmacovigilance legislation (Directive 2010/84/EU and Regulation (EU) No 1235/2010).	
447-465	22	Comment: Regulators have suggested that the known and unknown (but anticipated by mechanism of action) risks should be addressed in the PASS and RMP activities. Proposed change: We suggest this section be strengthened to take the regulators suggestions into account.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
449-465	7	Comment: It is suggested that Section 7 provides the rationale for the need for enhanced pharmacovigilance, i.e. due to the lack of data supporting each indication at initial approval. The importance of unique identification, traceability and effective pharmacovigilance should be further emphasised. Additional emphasis could be added related to monitoring for anticipated reactions (including rare ones), predicted due to the mechanism of action or experience with the reference product.	Accepted. The wording has been changed.
451-457	20	Comment: If the biosimilar applicant obtains indications based on extrapolation of data, it is recommended that additional post approval studies be required to confirm efficacy and assess safety in the extrapolated indications, for example in different tumor types. Comment: The need to monitor immunogenicity should be emphasised. Evaluation of immunogenicity should address: how to identify immunogenicity risk including secondary loss of effect in naive patients, any loss of effect not in naive patients, evidence of antibodies (neutralising vs. non-neutralising).	Not accepted. This should be assessed on a case-by-case basis and should be described in the RMP as it is currently included in the guideline. Accepted. The wording has been slightly changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
454	20	Comment: For clarity, insert "including long term safety data" Proposed change: "Safety in indications licensed for the reference mAb that are claimed based on extrapolation of efficacy and safety data, including long term safety data."	Accepted.
455	21	**Comment**: clarifying comment **Proposed change (if any):**efficacy and safety data including long term safety data	Accepted.
458	22	**Comment:** We ask the following statement be further clarified**,** "Pharmacovigilance may have to exceed routine pharmacovigilance and may have to involve more standardised environments."	Accepted. The wording in the guideline has been changed.
458	20	Comment: **"***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*."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The pharmacovigilance plan and post-authorisation measures should be no less stringent than for the reference product. The applicant should address risks known from the safety profile of the reference mAb and unknown risks anticipated by the mechanism of action in the PASS and RMP activities. Participation in registries should be a requirement, given the severity of the disease conditions.	
458-459	15	Comment: Please provide further clarity with regards to the term "standardised environment" in the context of the sentence, "The concept [on how to further study safety in a post-authorisation setting]…may have to involve more standardised environments."	Accepted.
458-459	17	Comment: Biosimilar products will have been extensively characterised showing no meaningful differences in comparison to the reference product and comparable efficacy and safety. Therefore, the pharmacovigilance rules applicable to biological products should be the same for biosimilar products. It is not clear what is meant by "more standardized environments". We suggest clarifying by referring to the implementing measures of the new EU PhV legislation.	Partly accepted. Pharmacovigilance rules for biosimilars are indeed the same as for other biologicals. This is included in the first paragraph of this section and reference is made to the general Pharmacovigilance legislation and guidelines. The wording "standardized environment" is further clarified in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The concept ~~may have to exceed routine pharmacovigilance, and may have to involve more standardized environments~~ **should follow the same pharmacovigilance rules as applicable to any biological product and take into account pharmacovigilance guidelines and measures following the implementation of the new EU Pharmacovigilance legislation** **"In considering any specific safety concerns it is likely that the MAH will have to go beyond routine pharmacovigilance. Where possible the MAH should provision to use standard data capture mechanisms to ensure accurate and consistent safety data capture / review."**	
459	7	Comment: Clarification is requested regarding the term "standardised environments" in the context of the sentence, "The concept [on how to further study safety in a post-authorisation setting] … may have to involve more standardised environments."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
459 - 460	6	Comment: „In addition, participation in already existing registries should be explored and presented as part of the Risk Management Plan." Proposed change (if any): Instead, participation in existing registries should be required due to the clinical program focusing on establishing biosimilarity rather than confirmation of efficacy and safety in the patient population. Thus the wording should be changed to: "In addition, participation in already existing registries should be ~~explored~~ – required and presented as part of the Risk Management Plan."	Partly accepted. Participation in already existing registries is recommended.
459-462	10	Proposed change (if any): Insert "e.g. disease registries" to ensure no confusion with blending post-authorisation safety data from the reference and the biosimilar products under the same registry. Proposed change (if any): Insert "and should not be dissimilar to the extent of the existing risk management plan already in place for the reference product".	Not accepted. Also for drug registries the inclusion criterion should be treatment with a particular active substance and not with one particular biological marketed by one company. Traceability is important in this context. Accepted with regard to the Pharmacovigilance plan.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
463	2	Comment: The first sentence is unclear. Proposed change (if any): Delete first sentence and rewording of the second: Recording the medicinal product (brand name) used by the physician should be envisaged to allow traceability of rare side effects.	Partly accepted. The statement currently included in the guideline has been amended to stress the importance of traceability.
463-465	21	**Comment:** Need to clearly identify also biosimilars to brand name. Biosimilars need to follow at minimum the same PV required as new biologics (and a black symbol is to used in the PI) **Proposed change (if any):** Provide more detailed guidance and reasoning that there needs to be a clear naming system for all biologics, including biosimilars.	Not accepted. This is outside the scope of this guideline.
463-465	22	**Comment:** Use of brand name and unique identification should be more than a recommendation. They are essential parts of effective pharmacovigilance and it is suggested this is further emphasised. It is important in the post-approval phase to distinguish easily between the biosimilar product and the reference product so that it is clear which product a patient has received. A record of the brand name, manufacturer name and lot number is essential to traceability and	Partly accepted. The wording of the guideline has been amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the conduct of effective pharmacovigilance. The draft guideline should be amended to take account of the recommendation in Dir 2010/84. *i.e.* that the product name and the batch number (lot number) should be recorded. **Proposed change:** We suggest the revised text:~~"Recommendations like recording the brand name of the drugs used by physicians, could be taken into account to reinforce traceability."~~ **"The product labelling should include a statement that the brand name of the medicinal product as well as the non-proprietary name, manufacturer's name, and lot number should be recorded when a medicine is administered or dispensed to a patient."**	
463-465	20	Comment: It is important in the post-approval phase to distinguish easily between the biosimilar product and the reference product so that it is clear which product a patient has received. The draft guideline should be amended to take account of the recommendation in Dir 2010/84. i.e. that the product name and the batch number (lot number) should be recorded EBE considers that a record of the brand name, manufacturer's name and lot number is essential to	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		traceability and the conduct of effective pharmacovigilance. The EMA could also explore additional identifying measures, such as requiring a unique prefix or suffix to be added to the INN attributed to the innovator. Proposed change: ~~"Recommendations like recording the brand name of the drugs used by physicians, could be taken into account to reinforce traceability.~~ The brand name of drugs used by physicians, the manufacturer's name and the lot number should be recorded."	
464 - 465	4	Comment: Traceability can be further improved by collection of the batch number of the administered biological. Proposed change (if any): Recommendations like recording the brand name and batch number of the drugs used by physicians, could be taken into account to reinforce traceability.	Accepted.
464-465	7	Comment: Whilst supportive of the statement "Recommendations like recording the brand name of the drugs used by physicians, could be taken into account to reinforce traceability", we would suggest re-wording to clarify that this would need to be managed by the local	Not accepted. The sponsors have an important role in the traceability of biologicals with regard to the collection of spontaneous reports and ADRs reported during studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		healthcare professional as sponsors would not have the means to enforce this requirement.	
464-465	17	Comment: The issue at stake here is to be able to link suspected adverse events to the correct biological product. It is consequently important to be able to clearly identify any biological medicinal product. The ADR reports must therefore include the name of the biological product together with the batch number. These reporting rules are the same for all biological products, as laid down in the new EU Pharmacovigilance legislation. The terminology 'brand name' may be understood as 'invented name'. Therefore the terminology 'name' should be used in line with Article 1 (20) of Directive 2001/83/EC as amended Proposed change: Applicants are recommended to follow further developments in the field 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.~~ **In line with the new Article 102 (e) of the amended Directive 2001/83/EC, Member States shall ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number.	