25 January 2018
EMA/CHMP/772616/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005 Rev. 1)

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

Stakeholder no.	Name of organisation or individual
1	Biotechnology Industry Organization (BIO)
2	European Biosimilars Group (EBG),
3	Amgen Ltd
4	Apotex Inc.
5	CELLTRION.Inc
6	AET BioTechnologie GmbH
7	F. Hoffmann-La Roche Ltd
8	EBE (European Biopharmaceutical Enterprises)
9	PharmaBio Consulting
10	Novartis International AG
11	European Coalition to End Animal Experiments (ECEAE)
12	Dr Ami Arieli, on behalf of European Parkinson's Disease Association
13	Pharmaceutical Product Development, LLC (PPD)
14	EuropaBio
15	Farmindustria
16	H. Schellekens, Departments of Pharmaceutical Sciences and Innovation Studies, Utrecht University
17	Medicines Evaluation Board, Netherlands
18	Pfizer
19	SciencePharma
20	The Janssen Pharmaceutical Companies of Johnson & Johnson

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the revised "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)." BIO commends EMA on the update of this Draft Guideline, which provides an important international precedent for the development and regulation of biosimilar biological medicinal products. 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 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. In general, BIO agrees that a stepwise approach is desirable in biosimilar development, beginning with physicochemical similarity before commencing non-clinical and final clinical development. BIO also agrees that '*the nature and complexity of the reference product has an impact on the extent of the (non-) clinical studies to confirm biosimilarity,'* however, we strongly believe that it is ultimately the degree to which the reference product can be elucidated, in terms of both its physiochemical properties at its	General remarks, no action needed

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	molecular level and its mechanism of action (MoA), that will have an influence on the amount of work required to confirm biosimilarity. While BIO considers extrapolation between indications an important consideration underlying the biosimilar framework, BIO strongly believes that it is important to ensure that each extrapolated indication is fully justified. BIO believes that it is clear that additional evidence will usually be required, although it may differ depending on clinical experience, available literature data, MoA of the active substance of the reference product in each indication, and the receptors involved. Such additional evidence and justification are necessary to demonstrate separately the safety and efficacy of each of the extrapolated indications. This general principle is set out in the Annex to Directive 2001/83, as amended, and we ask that the competent authorities follow it and carefully review the justifications provided by the biosimilar applicants. BIO appreciates this opportunity to comment on the revised "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/ 2005 Rev. 1)." We would be pleased to provide further input or clarification of our specific, detailed comments, which follow in Section 2, as needed.	
2	EBG appreciates this current draft version of the guideline on the non-clinical and clinical requirements for the development of biosimilar products. It is in line with the current thinking of the EU regulators who have shaped the regulatory framework for biosimilar products in a pioneering role. We welcome that the strong scientific principles laid down in this draft guidance are in line with those of the guideline for biosimilar mAbs which took the science-based development of biosimilar	General remarks, no action needed

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	products to the next level. With the revision of this guideline the leading role of the European regulatory framework for biosimilars will be further extended and strengthened. Please find our detailed comments below.	
3	Overall comment Amgen welcomes the opportunity to comment on the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev.1'. Amgen is both an innovative biologic developer and a biosimilar developer and we therefore consider that we are well placed to provide balanced and scientific comment on this guidance without pro-originator or pro-biosimilar bias. In general, we consider that this update to the guideline reflects the progress made over the last 8 years of biosimilar development and also the increase in confidence of the CHMP in the quality of the products that are registered via this regulatory pathway. However, we urge the EMA to remain pragmatic and vigilant in their approach as products of increasing complexity are developed and to continue to consider the legislative and practical requirement for providing non-clinical and clinical data to provide confirmation of biosimilarity prior to marketing.	**Pharmacovigilance**: The Risk Management Plan of a biosimilar product will follow the same principles as for other products.
3	Stepwise approach It is appreciated that the biosimilar applicants have to design and, if applicable, fine-tune their (non-)clinical development plans based on	Stepwise approach The step-wise approach to the development is recommended in the GL. Notifications of clinical trials to the

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	the results of the preceding physico-chemical and *in vitro* biological analysis of the biosimilar and the reference product. The degree of physico-chemical and biological comparability achieved in the early parts of the biosimilar development should determine the further studies to be conducted. Depending on the biosimilarity demonstrated for a certain biosimilar product, the guideline allows for a tailored (non-)clinical development which may differ between various applicants e.g. with regards to the size and types of the (non-) clinical studies needed. It is acknowledged that a stepwise approach is desirable in biosimilar development beginning with physiochemical similarity before commencing non-clinical and final clinical development. Indeed, this principle is strongly recommended throughout biosimilar guidance documents, however we consider that the concept needs to be developed further to ensure that the principle is actionable within processes at the national agencies and the EMA as currently clinical trial information is being reviewed at a national level while the complete dossier is reviewed at a central level. Clearly the stepwise process must take place during development however it is not within the scope of the national agencies to comment on the approach taken by the applicant during development.	national competent authorities are beyond the scope of this GL.
3	Data requirements While we agree that the design flexibility inherent in the biosimilar approach is such that the data package necessary to demonstrate biosimilarity will differ from biosimilar product to biosimilar product, we consider that it is paramount to ensure that sufficient work has been conducted in the pre-marketing setting to ensure that biosimilarity is demonstrated to such an extent that there is high	Data requirements General remarks not warranting modifications to the text. The risk management plan may contain post-marketing safety and efficacy studies (PASS and PAES).

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	confidence that a wide range of post-market comparative effectiveness evaluations will support this finding. Indeed, the draft guideline on non-clinical and clinical issues states that 'A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy.' As with innovative products, there should be no scope for indications to be approved for use without sufficient data to support it. Post-marking safety studies must not be used to replace those conducted in a pre-marketing setting.	
3	Labelling We believe increasing transparency, including through product labels, is the best way to promote accountability and foster confidence in biosimilars among the HCP community. It is suggested to include a high-level paragraph on the subject of SmPCs for biosimilars. Product labelling should be transparent and clear, summarising clinical data submitted for approval (including comparative clinical data and immunogenicity), enabling prescriber and patient to make informed decision on use of product. In order to cater to the specific nature of biosimilars, the label should contain a combination of information on both the biosimilar and the Reference Product. This would be prudent based on suggestions in the draft guideline that it may be permissible to have small (unintended) differences which while they do not contradict the principle of biosimilarity may differ from the reference medicinal product. If the agency is intending to apply the generic approach to labelling for all biosimilars approvals such that the SmPC contains no specific	Labelling: Labelling is out of the scope of the GL. The content of the SmPC of biosimilars is described in the template of the Quality Review Group of EMA. In general, the summary of product characteristics should only contain information that is important for the appropriate use of a product. Data on the physico-chemical, structural and *in vitro* functional as well as (non) clinical comparability studies are available in EPARs.

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	information gathered during the biosimilar development, in practice it will be difficult for all interested stakeholders (including both patients and health care professionals) to make evidence-based decisions on key topics such as switching of products but instead implying indirectly that the biosimilar is a generic product. Furthermore, labelling of biosimilars as generics strongly infers to prescribers that these products are interchangeable with their reference products because generic products are by definition interchangeable with their reference products and also have identical labels. Although the subject of labelling is not directly related to this guideline it is in many ways the summary communication means for the assembled non-clinical and clinical information and a target product label informs the nature of the clinical development approach selected. We urge the agency to clarify its position on labelling of biosimilars in concert with non-clinical and clinical issues and develop to specific guidance for biosimilars in consultation with all stakeholders.	
3	**Compliance with the current legislation** It is noted in the guideline that: 'Normally, comparative efficacy trials are required for the demonstration of clinical comparability.' However, in cases where comparative efficacy trials can be omitted due to the presence of suitable biomarkers, we consider that clarification is required on the amount of clinical safety and immunogenicity data which will still be required as part of the assessment dossier. Also, we consider that it is not possible under the current framework for any biosimilar applicant to entirely skip the need to provide an "appropriate" amount of non–clinical and clinical efficacy and safety data. The draft guideline indicates that clinical efficacy studies could be	**Compliance with the current legislation**: The draft guideline in compliant with the legislation. **Compliance with the legislation** The current guidance and the present draft overarching GL guideline are compliant with the legislation. The present GL as well as the product-class-specific guidelines will give further guidance of non-clinical and clinical studies.

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	avoided based on 'similarity of physicochemical characteristics and biological activity/potency of the biosimilar' in addition to comparative PK data. It is our view that the regulatory framework, including the annex to the Directive, requires a submission of both module 4 AND module 5 data. Hence a submission without any module 4 or module 5 data would arguably not be aligned with the framework outlined in the Annex to Directive 2001/83/EC as amended which states that: *When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.* *— Information to be supplied* ***shall not be limited to Modules 1, 2 and 3*** *(pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.* *— Due to the diversity of biological medicinal products,* ***the need for identified studies foreseen in Modules 4 and 5 shall be required*** *by the competent authority, taking into account the specific characteristic of each individual medicinal product.* While we agree that in some circumstances, an accepted surrogate PD marker may be used as confirmatory of similar efficacy profile, we consider that under current EU legislation results of clinical efficacy and safety data (not PK data only) are required for a biosimilar	

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	dossier to be valid and therefore the approach outlined in the draft guideline which indicates that it may be allowable to waiver clinical efficacy and safety trials (in their entirety) is not possible, regardless of the complexity of the molecule. Finally, due to the potential difference in immunogenicity between different molecules (biosimilar and reference product) we consider that immunogenicity should be investigated for all biosimilars in a sensitive pre-marketing setting.	
3	Extrapolation We consider that extrapolation between indications is a key underlying feature of and principle within the biosimilar framework. However, we consider that it is important to ensure that each extrapolated indication is fully justified and that it is clear that additional evidence will be required, although the nature of this additional evidence differ depending on clinical experience, available literature data, mechanism of action of the active substance of the reference product in each indication and on the receptors involved. Such additional evidence and justification are necessary to demonstrate separately the positive benefit/risk ratio of each of the extrapolated indication. This general principle is set out in the Annex to Directive 2001/83, as amended, and the competent authorities should follow it and carefully review the justifications provided by the biosimilar applicants.	Extrapolation No comment needed. The GL is compatible with the comment.
3	Immunogenicity It should be noted that neutralising antibodies are not the only type of antibody that can be raised by an immune response to a drug that	Immunogenicity The present draft GL should be read with specific GLs for the assessment of immunogenicity. The model for comparing

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	can have an effect on the efficacy of the drug. Binding and clearing antibodies can affect efficacy as well, making the drug less efficacious for that subject. Major quantitative differences in the prevalence of antibodies with relevant clinical effects on efficacy may contradict the biosimilarity concept as, on a population level, the efficacy profile of the product would be superior. Subset analysis for sensitivity of a comparison in efficacy in ADA-negative patients should exclude the obligation of the sponsor to justify the similarity of the product at the population level. Finally, data from many approved biologicals indicate that immunogenicity differs from indication to indication. It is thus more appropriate to assume that immunogenicity is likely to differ across indications rather than to assume that it will not. Therefore it is prudent that biosimilar manufacturers are required to provide clinical assessment of immunogenicity in the most sensitive patient population for that purpose (e.g. no receiving immune suppression or concomitant chemotherapy), even if it is a different patient population from that used to demonstrate comparable efficacy. This data should be included in the marketing authorisation application to inform the risk in those indications at the time of extrapolated approvals.	the efficacy, safety and immunogenicity should be sensitive to detecting differences. Immunogenicity: An analysis of antibody-negative patients would normally not be helpful to study comparability. As stated in the draft GL, it might be useful to clarify the cause of a seemingly better efficacy of the biosimilar but not the other way round. It is often impossible to know whether one indication is more suitable than another. Nevertheless, the selected indication must be suitable to study immunogenicity.
3	Populations and concomitant medications We consider that it is important to be clear that it is the study population and the endpoint chosen in efficacy studies will be the sensitive to detect potential differences if they exist. Special consideration should be taken to specific patient populations for which the reference product is authorised, including any concomitant	**Populations and concomitant medications** No comments needed

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	medications usually prescribed to this group of patients and the incremental effect size of the reference product based on the endpoint studied to ensure there is a comparable increased efficacy by the biosimilar and rule-out 'no effect' or placebo-effect statistically as well as a clinically meaningful difference beyond that minimal requirement.	
3	PD fingerprinting concept The draft guideline alludes to a comprehensive comparative 'PD fingerprint profile' that may be sufficient to allow some products to avoid the need for comparative clinical efficacy study: 'A combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability.' Although it is acknowledged that this approach is an extension of the PD concept that is already discussed in detail in published guidelines, this concept is not scientifically appropriate for all classes of biologics and their biosimilars. As such, we do not consider that this is a useful or helpful concept for this guidance, as it should only be considered on a case-by-case basis depending upon the number of relevant PD markers and the structural and functional complexity of the molecule in question and not as an overarching principle for biosimilarity. We suggest that the EMA should either omit reference to this concept from this guidance or if it remains in the final guidance, that EMA should add additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy	**PD fingerprinting concept** There is limited experience in the "fingerprinting concept. Therefore, it is advised to discuss the use of fingerprinting approach with the authorities. Thus, it is a case-by-case recommendation. PD fingerprinting: This would be exceptional and the draft GL recommends a consultation with regulatory authorities.

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5	The section on pharmacovigilance of biosimilars in the proposed draft of the guideline is really welcomed. Demonstration of safe and satisfactory safety and immunogenicity profile with biosimilar products is an essential prerequisite for licensure and postapproval life cycle of the product. The scope and size of the biosimilar safety database will be relatively limited pre-approval and therefore robust RMP and pharmacovigilance activities should be in place. However from biosimilar developer perspective the scope and intensity of post-approval pharmacovigilance should be proportionate and not to result in measures which are either exceeding those with the reference product or become both unfeasible or impractical. The main driving reason for development of biosimilars is to ensure cost-savings for the EU healthcare. Conduct of any post-approval studies is not without their cost burden to developers and in turns to healthcare providers. Therefore a proportionate and cost-effective use of different pharmacovigilance tools should be encouraged. Pragmatic and non-costly solutions will be beneficial to all stakeholders. It should be noted that the guidance encourages developers to participate in already existing pharmacoepidemiological studies with the reference product. There is risk that during post-approval there will be constant and mandatory comparison of the safety profile between biosimilars and reference whilst the products can undergo independent life cycles, have different extent of use in approved indications and different regional and country-specific uptake. Furthermore, there are some inherent limitations in different pharmacoepidemiological methods. Biosimilar developers are seeking CHMP and PRAC consideration in	In general, the pharmacovigilance requirements of the biosimilar are the same as for any other biological. Applicants for a biosimilar should always submit a Risk Management Plan, which should contain the topics as described in the respective PhV guidelines. This guideline describes the topics which are specific for biosimilars. The need for additional PhV activities should indeed be assessed on a case-by-case basis taking into account the information obtained during the pre-approval studies of the biosimilar and the information obtained with the reference product. The GL encourages Applicants to participate in already existing pharmacoepidemiological studies. The potential risks as described by the stakeholder are acknowledged and the primary aim of participating in already existing pharmacoepidemiological studies might not be to compare the safety profile between biosimilar and reference product but to learn more about specific adverse events, e.g. registries with TNF-alpha inhibitors have added important information about specific reactions, e.g. TB and malignancies. Information on these reactions with patients treated with the biosimilar will add important information about the rare adverse events for the group TNF-alpha inhibitors in general.

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	developing pragmatic, feasible, cost-efficient and yet prudent pharmacovigilance framework around biosimilars which could benefit to all EU stakeholders.	
6	Revision and in particular restructure of Section 4.3. as compared to the same section of *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* is considered to make the revised guideline more comprehensive.	The structure of section 4.3 of the present GL is in fact quite similar to the structure of section 4.3 of the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues.* However, since the spectrum of possible active substances covered by the present GL is much wider, several additional aspects had to be mentioned in the context of section 4.3.
8	Overall Comment EBE welcomes the revised draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues' EMEA/CHMP/BMWP/42832/2005 Rev. 1 This draft document reflects in summary the comprehensive expertise gained by EMA over the last 8 years of biosimilar development and we agree with the general principles. However, we would like to submit for your consideration the following points, which we hope you find helpful. For example key points on the capturing of safety data where PK/PD studies may confirm clinical efficacy are missing as can be seen in our general and in specific comments. It is assumed that the guidance is intended to cover over-arching principles and therefore should not be very detailed as further detail is covered in class specific guidance. However, as this is not clearly stated in Section 2 and, in case the intent is to provide detailed guidance, we have included appropriately detailed comments in the submission.	The hierarchy of the guidelines is clear. After the revision of the overarching GLs, the CHMP will review the product class-specific GLs for any discrepancies. Biomarkers: The current GL has a broad definition of a suitable biomarker. It is difficult to give detailed descriptions because of the heterogeneity of potential biomarkers. The key is the relationship to clinical efficacy. The burden of evidence is on the Applicant. **Step-wise approach** and national regulatory agencies: This is beyond the scope of the present GL. It is expected the new clinical trials regulation will facilitate harmonisation of the requirements in multinational clinical trials. While the *in vivo* non-clinical testing is not recommended as a routine, such studies might be appropriate as described in the draft GL. EMA has provided and will continue to provide training and information to experts of the national competent authorities,

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	Use of biomarkers It is stated that the availability of suitable biomarkers may abbreviate the (non-) clinical development. A definition of what constitutes a 'suitable biomarker' should be added to the text including i)biomarkers used in the development of the reference product or ii) biomarkers which have a patho-physiological link to the therapeutic drug effect of the biosimilar. Furthermore, it is not clear how suitable biomarkers would be of use in the non-clinical development. Further clarification around the principles of biomarker use (where they are not accepted surrogates) within both non-clinical and clinical development is required for this concept to be fully utilised. Stepwise approach It is appreciated that the biosimilar applicants have to design and, if applicable, fine-tune their (non-)clinical development plans based on the results of the preceding physico-chemical and in vitro biological analysis of the biosimilar and the reference product. The degree of physico-chemical and biological comparability achieved in the early parts of the biosimilar development should determine the further studies to be conducted. Depending on the biosimilarity demonstrated for a certain biosimilar product, the guideline allows for a tailored (non-)clinical development which may differ between various applicants e.g. with regards to the size of the (non-) clinical studies needed. It is acknowledged that a stepwise approach is desirable in biosimilar development beginning with physicochemical similarity before commencing non-clinical and final clinical development. Indeed, this principle is strongly recommended throughout biosimilar guidance documents, however we consider that the concept needs to be developed further to ensure that it is workable at the national level while development is ongoing, as it is not within the scope of the	**PD fingerprinting**: It is the Applicants duty to convince regulators of the validity of their approach (e.g.scientific advice). This is stated in the GL.

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	national agencies to comment on the approach taken by the applicant during development. The duty of the EMA/CHMP to check, during the central marketing authorization procedure, that R&D programs comply with good clinical practices and ethical principles (as per the Annex to Directive 2001/83, as amended), could play a role for ensuring that an appropriate stepwise approach is followed by biosimilar applicants. Some members have encountered local ethics committee concerns about degree of pre-clinical safety testing for biosimilars. Such local reviewers may not yet be fully informed about EU regulators' current thinking and may request additional animal testing prior to proceeding into human testing, even though such safety testing is not indicated in this draft guidance. Therefore we would like to suggest that such a recommendation is: (1) Included into the Scientific Advice document so that it can be shown to local HAs and ECs, and (2) Also distributed and made known within the entire EU regulatory world among all member states. **PD fingerprinting concept** The draft guideline alludes to a comprehensive comparative 'PD fingerprint profile'. Although it is acknowledged that this approach is an extension of the PD concept that is already discussed in detail in published guidances, this concept is not scientifically appropriate for all classes of biologics and their biosimilars. As such, this approach should be considered on a case-by-case basis We suggest to either omit reference to the PD fingerprinting concept or, if it remains, that additional discussion explaining its limitations and providing specific criteria for use particularly the methodology to	

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	create a sensitive and specific set of PD markers where none individually is sensitive or has specificity. Furthermore, it would be of interest to also address how extrapolation would be handled if comparable efficacy is demonstrated on the basis of a PD markers only and if and how the need or wish to extrapolate would affect the design and parameter choice for such a study as described above.	
9	PharmaBio Consulting finds this is a well written guideline in nonclinical and clinical efficacy aspects, but more information is needed on the safety and pharmacovigilance (PV) parts. These are strongly emphasised for biosimilars and deserve more comment especially as a result of the new PV regulations. Also, that biosimilars carry an inverted black triangle requiring closer surveillance from 2013 differentiates them from originators from the standpoint of the patient and prescriber. This needs to be put in perspective by the EMA. Furthermore, from an international, e.g FDA, perspective the new symbol will be a point of divergence. Already the burden of clinical evidence of biosimilarity in EU is substantial. If a US product is bridged to EU by a reduced study, will the postapproval commitments be greater that if the product is first EU approved? This needs to be addressed in 2013 with the begginings of FDA/EMA collaboration today.	This guideline provides general information on the requirements related to clinical safety and pharmacovigilance for biosimilars. Regarding clinical safety and PhV for specific product classes reference is made to the product specific guidelines. The new PhV regulations fully apply to biosimilars and there should be no repetition within this guideline. This scientific guideline provides guidance on PhV topics specific for biosimilars and should also be read as such, with the exception of the issue described in lines 404-408. Due to the importance of identifiability this general remark is included in this guideline. Discussion on the black triangle is beyond the scope of this scientific GL. FDA and EMA are collaborating in order to harmonise the requirements. However, sometimes, this will require legislative changes that are beyond this GL.
10	Novartis appreciates this current draft version of the guideline on the non-clinical and clinical requirements for biosimilar products. It is in line with the current thinking of the EU regulators who have	General comments, no response required.

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	shaped the regulatory framework for biosimilar products in a pioneering role. We welcome that the strong scientific principles laid down in this draft guidance are in line with those of the guideline for biosimilar mAbs which took the science-based development of biosimilar products to the next level. With the revision of this guideline the leading role of the European regulatory framework for biosimilars will be further extended and strengthened. Please find our detailed comments below.	
11	The European Coalition to End Animal Experiments (ECEAE) welcomes the inclusion of a stepwise approach to the evaluation of biosimilars that considers animal tests as a last resort. While we appreciate the introduction of a stepwise approach to include an evaluation of whether or not animal studies are required, we feel that the guideline is still overcautious in its recommendations given that animal tests are rarely needed and the significance of their results is highly questionable. During the biosimilars workshop that was held at the European Medicines Agency in London on October 31st 2013, many stakeholders voiced the general consensus was that the value of animal tests in this area was questionable. Here a few examples of quotes from various speakers at the workshop: "*I don't believe that animal models inform immunogenicity in humans. Most animal models are kind of contrived anyway. Evidence from animal models is not definitive; it merely gives us something to look at early on. Immunogenicity in animal models doesn't*	Biosimilarity is an evolving concept. The current draft represents a clear change in the relative importance of *in vitro* and *in vivo* non-clinical studies, i.e. the step-wise strategy for non-clinical development. It does not require *in vivo* non-clinical studies automatically. In fact, the GL clearly points out that, in accordance with the provisions of the *European Convention for the Protection of Vertebrate Animals* used *for Experimental and Other Scientific Purposes* and Directive 2010/63 EU, the 3R principles (replacement, reduction, refinement) have to be observed and *in vivo* animal studies should only be considered on a case-by-case basis if they are clearly necessary to provide complementary information needed for the biosimilarity exercise and which cannot be obtained otherwise. The current experience from EMA scientific advice is that *in vivo* non-clinical studies are very rarely required. The development of a biosimilar starts always with physico-chemical, structural analytical tests and *in vitro* functional tests some of which could be regarded as *in vitro* non-clinical tests as well.

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	necessarily translate to immunogenicity in humans". "*If the molecules were so different that they would show different immunogenic responses in animals, these differences would also be picked up by analytical techniques, therefore animal studies would not add anything to the assessment".* *"It is hard to determine if the differences (found in animal studies) are meaningful therefore I don't think animal studies should be done".* *"I am not advocating animal studies – most animal studies for biologics are a waste of time anyway".* *"Animal data has shown to be more acceptable for ethical committees – education of national regulators and ethical committees on biosimilars is crucial for avoiding unnecessary studies".* Analytical methods at the first step Many recent articles have placed a high emphasis on specialised analytical technologies including MS, NMR and HDX-MS, which are highly sophisticated methods that are capable of measuring both physicochemical and functional similarities of proposed biosimilars; "*Extensive physicochemical and biological characterisation using an array of standard and advanced analytical tests is a key aspect of the approval process for biosimilars*". Gascon et al., 2013). The US FDA appears to be heavily reliant on analytical studies, therefore the importance of these methods should also be highlighted by regulators in Europe; "*The FDA has decades of experience with approving manufacturing changes for biologic and small molecule medications by relying on analytics, and rarely are clinical studies*	As pointed out in the comment, the decision of when biosimilar is similar enough is made on case by case basis on basis of all available data. The knowledge of the variation between batches of the reference product will guide the decision making. It is in the interest of all stakeholders that unnecessary animal testing is avoided. The ICH is beyond the scope of this GL.

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	required […] As the FDA moves to state-of-the-art test tube techniques to evaluate biosimilars, health plans may need to gear up with expertise in laboratory technology and analytic techniques". (Reinke, 2012). A battery of highly specific analytical methods can be used to produce a robust comparison of a biosimilar to the original drug. The more comprehensive the data package, the less likely animal tests will be needed. If confidence can be established using these techniques than the product can be allowed to move straight into clinical trials which will always provide significantly more reliable data than animal tests. We therefore suggest that the use of analytical data from these methods should be included as Step 1 before in vitro studies. These techniques can establish the comparability between a biosimilar and a reference product. If a drug is deemed to be analytically highly similar to the reference drug then there is no reason why an animal test should be recommended before moving to clinical trials. "*In the case of biosimilars, one possible future decision – which would have obvious economical consequences – could be that manufacturers are not required to run exhaustive clinical trials on the basis that their drug is deemed to be analytically highly similar to the innovator drug*". (Berkowitz et al., 2013). "*Modern analytical technology is rapidly advancing the characterisation of biopharmaceuticals […] it is hoped that both the biopharmaceutical industry and regulatory agencies will fully realize and appreciate the ramifications of the emerging bioanalytical*	

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	technologies available to them, as well as existing technologies whose potential has not been fully exploited, to help monitor the safety of biopharmaceutical products […] Regulators will need to keep abreast of developments with these methodologies and require submitters of products to include analytical methods that are information-rich. In so doing, however, regulators will need to understand the capabilities and limitations of these advanced analytical tools and keep track of their improvement as these new tools are further developed". (Berkowitz et al., 2013). Examples of commonly used and recommended analytical technologies should also be included and a brief description provided. For example, mass spectrometry (MS) is a valuable tool for investigating protein modifications while specialised analytical methods such as x-ray crystallography and nuclear magnetic resonance (NMR) can be used to determine high-order protein structures and can provide useful comparability assessments. Protein labelling methods (e.g. HDX-MS) can also be used to detect small changes in high-order structures and can even provide information as where the change has occurred. "*Because HDX-MS can reveal details of the higher-order structure of proteins, as well as protein dynamics, the method has the potential to become an important tool for studies assessing comparability between innovator products and their biosimilars".* (Berkowitz et al., 2013). We therefore suggest that submitters be required to conduct detailed analytical analyses before turning to regulators for a decision. Regulators should also be encouraged to keep up to date with these advancing technologies so that unnecessary testing can be avoided.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Manufacturing changes A commonly cited concern with biosimilars is that changes in manufacturing processes can lead to unwanted modifications of biologics that may cause unknown and harmful side effects. However, in practice this problem seems to be relatively rare and animal studies are usually not necessary to assess these changes; "*All stakeholders generally accept that these studies (preclinical and clinical) are rarely necessary for originator biologics that are making a manufacturing change and in fact in the past have been required by the FDA in fewer than 1-2% of cases*". (McCamish and Woollett, 2012). In any case, why is it not possible to ensure that manufacturing processes remain identical to those used for creating the innovator product? We have suggested that manufacturing process is considered in the new Step 1. Existing data? The value of looking at existing data or sharing data with other submitters/regulators should also be considered before animal tests are recommended. How similar is similar? It is not clear in the guideline how similar a biosimilar has to be to the original product for it to pass a comparability assessment. We understand that this will be assessed on a 'case-by-case basis', however we are concerned that if there is no set guideline or standard to explain what the cut-off point is, additional tests (including animal experiments) might be suggested when they are	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	not necessary. It is clear that no biologic can ever be identical to another, but it should be also be explained how far submitters are expected to go to demonstrate similarity. If the submitter has not bothered to carry out an extensive analytical analysis of their biosimilar or is unaware of the advancing analytical techniques and other alternative methods that are available then it should not be inevitable that animal tests will be recommended based on the absence of data. Similarly, if a wealth of analytical data is presented to a regulator but they are not up to date with the methodologies of these techniques then won't they ask for animal tests just to make sure? These concerns should be addressed by providing a clear rationale of how similar biosimilars have to be in order to avoid bias towards animal data or the overcautious recommendation of animal tests. ICH guideline We would like to take this opportunity to suggest that the EMA takes steps to encourage update of the related ICH guideline i.e. 'ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998) as soon as possible to reflect the outcome of this guideline and developments in the biosimilars industry.	
12	have read this interesting draft. It seems to be a straightforward paper. However, as a patient, I missed the referring to the patient's age. In my opinion, drug safety evaluated in clinical trials should be based on people (volunteers or patients) that are close in their oldness as much as possible to the age range of the target population.	The goal of the biosimilar development is to demonstrate similarity, not to repeat studies that were required from the reference product, including studies in special patient groups. However, it is expected that the developers will consider the age of the population, e.g. when extrapolating safety and efficacy from one therapeutic indication to another.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
14	EuropaBio welcomes the opportunity to discuss the revised 'Guideline on similar biological medicinal products containing bio-technology derived proteins as active substance: non-clinical and clinical issues' Overall, EuropaBio supports the main principles and methodologies outlined in the current draft version and in particular the following: • The strong scientific principles and risk-based and step-wise approach to determine the need for non-clinical in vivo data or clinical data • The criteria that drive the need for efficacy studies as well as recommendations on the design of efficacy studies. • The inclusion of the definition of a biosimilar product as this will help distinguish between high-quality biosimilar products developed and licensed according to the high European regulatory standards and "non-comparable copies" of biological products available in many other parts of the world. With reference to the discussion that took place at the workshop on October 31, we believe that the definition could be clarified (see our comments with lines 55-58) but should not otherwise be changed. If a change is contemplated, we suggest to also clarify in the guideline why biosimilars do not usually meet the conditions to be considered as a generic medicinal product (with reference to recital 15 of Directive 2004/27/EC and article 10.4 of Directive 2001/83 as amended) • The need to ensure that each extrapolated indication is fully justified and that it is clear that additional evidence may be required, depending on clinical experience, available literature data, mechanism of action of the active substance of the reference product in each indication and on the receptors involved. Objective criteria and clear proactive guidelines are needed to foster physician confidence in extrapolated	The definition of a biosimilar medicinal product is given in the overarching GL of similar biological medicinal products. The rules for **extrapolation** of safety and efficacy is spelled out in the GL. It should be noted that the "totality of evidence" concept is applied in the assessment of extrapolation. Stepwise development and clinical trials: The supervision of clinical trials is in the remit of national regulatory agencies. During the marketing authorisation process, the company assures that all clinical studies are conducted according to the GCP. EMA has the possibility of requesting a GCP-inspection PD fingerprint approach is currently an exceptional approach. Therefore, the GL recommends that regulatory authorities are consulted prior to conducting such studies. The interchangeability and product switches are indeed outside the remit of EMA and should be dealt with at a national level. It has therefore been deleted from the guideline. **Safety and abbreviated efficacy testing**: the GL gives a sufficient general guidance on safety requirements.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	indications. • The risk-based approach regarding the submission of immunogenicity data pre- or post authorisation. While we agree to these main principles, we have remaining concerns on the following aspects: • **The stepwise non-clinical and clinical development** needs to be developed further to ensure that it is workable with the national agencies and the EMA as currently clinical trial information is being reviewed at a national level while the registration dossier is reviewed at a central level. Clearly the stepwise process must take place during development however it is not within the scope of the national agencies to comment on the approach taken by the applicant during development. The duty of the EMA/CHMP to check, during the central marketing authorization procedure, that R&D programs comply with good clinical practices and ethical principles (as per the Annex to Directive 2001/83, as amended), could play a role for ensuring that an appropriate stepwise approach is followed by biosimilar applicants. • The draft guideline alludes to a comprehensive comparative '**PD fingerprint profile**' which may allow products to demonstrate clinical comparability on the basis of a comparative PK/PD study (line 280 'a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability'). Although it is acknowledged that this approach is an extension of the PD concept that is already discussed in detail in published guidances, this concept is not scientifically appropriate for all classes of biologics and their	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	biosimilars. As such, we do not consider that this is a useful or helpful concept for this guidance, as it should only be considered on a case-by-case basis depending upon the number of relevant PD markers and the structural and functional complexity of the molecule in question and not as an overarching principle for biosimilarity. • We do not consider that the principles of '**Switching' and 'interchange/interchanging'** fall within the scope of this guidance. As stated in the Questions and answers on biosimilar medicines, 27 September 2012, EMA/837805/2011, 'The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine.' The EMA/CHMP have consistently adhered to this approach since the first biosimilar was approved in April 2006 (and post approval) until now and refrained from taking any position as to whether or not the biosimilar can be switched or interchanged with its reference, including in the biosimilar EPARs. We believe that this approach is appropriate and therefore consider that it is not appropriate to mention these concepts in this guidance document and suggest removing this text. The notion that relevant differences between biosimilar and reference product should be excluded for both efficacy and safety (including immunogenicity) and that these concepts are not necessarily the same should be better worked out, particularly in situations when further abbreviated pathways are considered (e.g. a comparative PK/PD study for demonstration of clinical comparability or in case of extrapolation to more than one indication).	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
16	In the concept paper regarding this revision (EMA/CHMP/BMWP/572828/2011) there is only a very superficial statement regarding the impact of the revision. According to this statement only companies and regulators will be impacted by the revision. However the impact of this guideline goes beyond this. Guidelines influence the costs of biosimilar development which translates to pricing and drug prices determine accessibility. According to estimates the costs of biosimilar development are substantial and will only lead to a maximum of 50% reduction in price. For many biologics this will still limit accessibility, also in the developing world that considers the EMA guidelines as the main example. This situation demands a comprehensive impact analysis of the revision, including a detailed cost-benefit analysis. On the basis of the impact analysis the need for the revision and its actual content should be re-evaluated. In the same draft paper only regulators and pharmaceutical companies are called interested parties. Patients and medical professionals are also important parties for any CHMP guideline and should also be invited to comment the draft revision. Also independent scientist and their societies are interested parties. It is also advisable to invite representatives of these parties to participate in writing the draft revision. It may help to avoid the mistakes and unclear parts of the draft that lead to an inefficient review process. I expect that the comments of most parties will be rather redundant and concern the same mistakes in the draft. It is surprising to find only references to other guidelines in the concept paper. Also in the revision not a single reference to the scientific literature can be found. The CHMP and advising parties consider themselves scientific committees. Therefore they can be	Biosimilars and costs, impact on other regions: Guidelines for biosimilars are drafted according to the same principles as any other CHMP GLs. Costs are clearly beyond the scope of the GL. For time being, each region will define its own guidance for biosimilars. This GL presents the current view of the CHMP on development and assessment of safe and efficacious biosimilars within the EU legislative framework. WHO has provided guidance than can be applied in those regions where such guidance is not yet available. EMA is working for the harmonisation of the requirements at least in the ICH countries.. Stakeholders: The concept paper and the draft GL has been in a public consultation, including a public workshop. Patients, prescribers, and academics are welcome to send their comments. Scientific papers: CHMP and its working parties monitor the scientific literature during the process of GL preparation. However, it is not practical to add references since the GL covers the whole product development of biotechnology-derived proteins. In general, the scientific knowledge on biosimilars is accumulating during the product development and assessment. Much of these data have been confidential. The scientific literature is based of publicly available data. The recent attempts of EMA to increase transparency will narrow the gap between data that will be submitted and publicly available data.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	expected to adhere to a scientific approach. Any guideline or revision should be based on an extensive and public review of the scientific literature and any statement and assertion in the revision should be referenced by the appropriate scientific papers. This will allow the validation of position of the CHMP by the parties reviewing the revision.	
17	The *communis opinio* which can be derived from recent CHMP opinions and SAWP advices is, that the goal of a biosimilar is to develop a product which is highly similar to the reference product, and that therefore clinical data should be used to confirm this high similarity; these clinical data should not be used to justify 'significant' differences (like e.g. major changes in the glycosylation pattern). The same could be said for *in vivo* non-clinical studies. The current draft contains a number of places where the impression is given that significant differences can be negated as long as (non-)clinical data do not demonstrate a significant difference in safety or efficacy, despite such studies sometimes being insensitive in detecting relevant differences. The current draft appears to consider comparative randomised controlled trials (RCT) as the default for evaluating comparative efficacy. It is agreed that a biosimilar should have similar efficacy as the reference product. However, this does not necessarily imply a "full-blown" efficacy study i.e. RCT comparative trial. Efficacy may be deduced from comparative data on physicochemical and biological characteristics, including a complete functional assessment, similar pharmacokinetic profile and similar PD . As far as clinical data are concerned, based on case-by-case basis it may be justified that	Differences in quality and the role of clinical trials: The comment seems to imply that it is always possible to define a significant difference. This may often be the case since the regulators have a long experience in assessing differences between the versions of a given product. In addition, sensitive in vitro tests are available to study the functional impact of the observed difference. However, the relevance of these differences in vivo may be questionable. In this situation, clinical trials may be helpful. At the end, the biosimilarity is assessed on the basis of the totality of evidence and not on piecemeal basis. The GL contain the general elements that are needed for the development of a biosimilar product. It is complemented by product-specific guidance and CHMP scientific advice.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	efficacy data range from comparative PK, PK/PD, a limited clinical trial (e.g based on biomarkers) to a full blow RCT. It is considered up to the company to justify their data package with respect to efficacy. This principle may be more clearly expressed in the current document. Of note it may even be considered contra-productive to repeat the RCT that have been performed in the dossier of the reference product as this may not be the most sensitive way to show a difference when it actually exists See also detailed comments made below.	
18	**Overall Comments:** Pfizer welcomes the revised draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues' EMEA/CHMP/BMWP/42832/2005 Rev. 1 We agree with the overall principles however further clarity is needed in some areas highlighted below. **Scope** We propose to add some wording under 'scope' which explains what is intended to be covered by this general guideline on preclinical and clinical issues and how the overarching guideline relates to this as well as the class specific guidelines such as for biosimilar monoclonal antibodies. The non-clinical and PK section of this guidance is similar to the respective sections in the biosimilar monoclonal guideline. Should this be identical or is it intended to be an overview? If it's intended to be an overview this should be stated upfront. If there are differences which are supposed to be applicable to smaller biotech proteins this should be made clear upfront. The guidances should make clear when	The overarching GL represents the CHMP current view on the general aspects of the (non)clinical development of biosimilars of biotechnology derived proteins. The hierarchy of the guidelines is clear. The product class-specific GLs give more detailed guidance but do not overrule the general guideline. CHMP keeps revising its guidelines. This is the case for the entire set of the biosimilar GLs as well. The companies have always the possibility for scientific advice in case the interpretation of GLs is difficult. The development should be risk-based rather than based on product classes or single characteristics, such as molecular size. Step-wise approach: The comment deals with the clinical development. The non-clinical part presents the stepwise approach to non-clinical testing. The revised GL also emphasizes stepwise clinical development. The GL for Similar Biological Medicinal Products explains the overall stepwise development concept.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	requirements are targeted for smaller/simpler biotech products only and when reference is made to high level principles applicable to all biotech proteins. We believe that this guidance applies to all biotech proteins regardless of their complexity, however if this is the case it needs to be explicitly stated and we have proposed text in the specific comments section below. **Stepwise approach** The first mention of the stepwise approach to biosimilar development is not until page 7 of the guideline where it is referred to in the context of clinical studies. We believe that the stepwise approach to the entire comparative program should be explained upfront in the guideline and specific proposed text is included before the non-clinical studies section. **PK/PD study in replace of a Phase 3 equivalence study** Pfizer believe that this should apply exceptionally when all listed caveats are met however there is no mention of how safety and immunogenicity will be assessed in this scenario and we believe that clarity and guidance on this is necessary. We have made specific recommendations in the specific comments section below. **Immunogenicity** Pfizer agree that shorter follow up pre-licensing (e.g. 6 months might be justified based on the safety/immunogenicity profile of the reference product). However, further clarity is needed as to whether this applies to all classes of biosimilar products. We have proposed the inclusion of reference to available product specific biosimilar guidance based on the discussion at the EMA workshop on 31st October. **Extrapolation**	**Immunogenicity**: The GL states that the length of the follow up is normally one year for products with chronic administration but can be shorter if justified. The justifications should take into account the characteristics of the product and the experience from the reference product. The Guideline on Immunogenicity assessment of therapeutic proteins is valid for all therapeutic proteins, including biosimilars. Extrapolation: The chapter on extrapolation has been revised. The CHMP will apply “totality of evidence” when considering extrapolation. The GL does not advocate clinical trials in all therapeutic indications, except in cases when the mode of action of the product in different indications is different and when non-clinical studies are insufficient to demonstrate comparability.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Pfizer believe that the current wording in the guideline is misleading. The current wording suggests it may be necessary to perform a clinical study in each of the indications and we do not agree with this. If this were the case then it would likely be because the product was not shown to be biosimilar at the earlier stages and therefore couldn't be developed as a biosimilar. Alternative wording is proposed in the specific comments below.	
20	The Janssen Pharmaceutical Companies of Johnson & Johnson (referred to as Johnson & Johnson in these comments) are pleased to submit these comments on the Draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (Draft Guideline). Johnson & Johnson has expertise in a broad spectrum of disease areas, including anaemia management, immune-mediated diseases, oncology, cardiovascular disease, pain, neuroscience, metabolic disease, and virology. In addition, we are among the global leaders in biotechnology and have many years of experience with the development, manufacture, and post-marketing monitoring of biopharmaceutical products. As we noted in our 2011 comments on the related Concept Paper, Johnson & Johnson supports the CHMP's decision to review and revise its existing over-arching biosimilar guidelines. We appreciate the CHMP's consideration of these comments and its continued engagement with stakeholders as it revises these guidelines. The Draft Guideline contains many important features that promote patient safety and improve on the original 2006 Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (Original Guideline). We are concerned about a number of issues	This comment present general comments on the extrapolation and disagrees with the concept that a biosimilar product contains the same active substance as its reference product and requires more conservative regulatory requirements, including immunogenicity and extrapolation. The GL will not add to the regulatory requirements..Immunogenicity: Comparative immunogenicity studies are always required. The GL makes reference to extrapolation where the lack of safety studies, including immunogenicity, must be justified. The experience from new versions of reference products after a change in the manufacturing process suggests that immunogenicity is a very rare event. It is also known that the entry of immunogenic biosimilars into the market may be prevented by the pre-market immunogenicity testing.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	raised by the Draft Guideline, however, and respectfully request some changes that we believe would promote patient welfare. In particular, we believe the discussion from lines 326 to 413 should be revised to more closely reflect the fact that even if a biosimilar has the same amino acid sequence as its reference product, it does not contain the same active substance and, thus, may exhibit a different safety profile from its reference product. As explained below, therefore, even when clinical differences are not anticipated, protecting patient welfare will always require some comparative clinical immunogenicity testing of sufficient duration to assess important differences. Further, as the CHMP notes, "immunogenicity could differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified." As a result, extrapolation of safety and efficacy of a biosimilar to a new indication or clinical setting following highly limited or no clinical testing can carry significant risks to patients. We recommend a conservative approach to scientific justification of extrapolation and believe that robust post-market safety surveillance will be always necessary. [We generally support the comments submitted by European Biopharmaceutical Enterprises (EBE) and intend these comments to complement EBE's.]	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
36	9	Comment: Even when there is no evidence of immunogenicity affecting efficacy or safety such as with insulin's or growth hormones, or where the extent of immunogenicity can differ by indication as with mAbs without any relative impact, a rigorous study of comparative immunogenicity is required. Proposed change: Insert "Neutralising AB may not be known to have any influence on efficacy or safety but is particularly important in the comparability exercise."	The text has not been changed based on this comment. The present GLs on immunogenicity of therapeutic proteins contain sufficient guidance on the testing strategy for anti-drug antibodies. Guidance on the immunogenicity of insulin will be included in the product class-specific GL for insulins. The role of neutralizing ADAs is elaborated in the GL of immunogenicity of therapeutic proteins.
45	8	Comment: Reference should be made regarding similarity of product already authorised rather than marketed. Proposed change: Consider amending the text as follows: '…another one already authorised and which is either currently marketed or has been at some point after authorisation ("biosimilar").'	Point accepted and the text modified.
45	14	Comment:	Point accepted and the text modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Reference should be made to similarity of a product already authorised rather than marketed. Proposed change: …another one already authorised and which is either currently marketed or has been at some point after authorisation ("biosimilar").	
45	17	Comment: 'marketed' should be 'authorised'.	Point accepted and the text modified.
46	2	**Comment:** The non-clinical section addresses the in vitro study requirements and assesses whether in vivo pharmacodynamic or toxicological studies would be needed. **Proposed change:** The non-clinical section addresses the pharmaco-toxicological requirements of in vitro pharmacology and pharmacodynamic studies and cases when there is a need for additional in vivo toxicological assessment.	Not accepted. *In vivo* animal studies, if really needed (see definition in section 4.2), may comprise pharmacodynamic and/or toxicological studies as to be determined on a case-by-case basis.
47-49	2	Comment: Immunogenicity testing composes an inherent part of the development programmes of biologicals, including biosimilars. Consequently immunogenicity data needs to be submitted for all biologicals pre-authorization. As discussed in subsection '7. Pharmacovigilance' of the current draft guideline, the identified and potential risks associated with the reference and biosimilar	Not accepted. Immunogenicity is already an important part of the clinical safety and pharmacovigilance section of the draft guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products should be adequately addressed in the risk management plan, and immunogenicity should be specifically addressed in this context. **Proposed change:** The section on clinical safety and pharmacovigilance addresses clinical safety (including immunogenicity) studies as well as the risk management plan with special emphasis on studying the immunogenicity of the biosimilar.	
50-51	17	Comment: The term 'risk-based' introduces a concept that is not appropriate for the development of biosimilars. The aim is to produce a product that is similar, not to make a product with differences which may or may not introduce additional risks. In the current set-up of the draft it would be better to speak of a step-wise approach. Yet as we will comment in the non-clinical section, there is little use for the now proposed third step, i.e. animal studies and the second step is not really a separate step in development. Proposed change: ~~a risk-based approach~~ an outline for the design of non-clinical studies	Not accepted. It is agreed that the aim of a biosimilar development is to produce a product which is similar in efficacy and safety to its reference product and does not introduce any clinically relevant additional risks. To achieve this, the present draft GL recommends a step-wise approach, which includes a risk-based decision whether additional non-clinical *in vivo* animal studies are needed in case uncertainties remaining following analytical and *in vitro* non-clinical evaluation, which could block an initiation of clinical studies.
50-53	2	Comment:	The text has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In subsections 5.3. Efficacy trials and 5.4. Clinical safety of the current draft guidelines besides acceptable primary, secondary and surrogate endpoints, clinical safety (including immunogenicity testing), risk management plans and pharmacovigilance aspects are discussed. We are of the opinion that the executive summary should reflect more precisely the content of the above mentioned sections. Additionally it has to be highlighted that immunogenicity testing is normally part of the efficacy and safety studies. **Proposed change:** The current revision covers the following topics: a risk-based approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of primary and secondary surrogate endpoints (including surrogate endpoints) in efficacy trials; clinical safety, risk management plan, and pharmacovigilance; design of immunogenicity testing studies; and extrapolation of indications.	
51	7	Proposed change: Replace “choice of appropriate” with “choice of the most appropriate”	Not accepted. It may be difficult to say which endpoint as the most sensitive. It is sufficient to say “sensitive”.
52	7	Proposed change: Replace “surrogate endpoints” with “sensitive	In this context “surrogate” is appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endpoints" as specified in row 313	
55	3	Comment: The draft guideline includes a definition of biosimilars which could be confused by the reader to determine that a biosimilar contains a version of the active substance of the reference medicinal product only. We consider that the use of the word 'version' is not appropriate as in today's vernacular is more akin to one manufacturer making a process change as opposed to two competing products by different manufacturers even if the products have the same functionality. The subsequent text in the guideline mentions the need for the same posology and route of administration, but without the second sentence of the definition being read in conjunction with the first, it opens the definition of biosimilars as any product with a similar active substance. Formulation, route of administration, device and presentation are integral parts of a registered medicinal product and biosimilarity should be based on a comparison of the medicinal product as a whole. We therefore suggest that the definition of a biosimilar comprises both the first and the second sentence of this paragraph and removes the word version. We believe that the definition should not otherwise be changed for instance to add that a biosimilar is similar	The definition of the biosimilar product will be in line of the GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to a “known” product or substance. If such a change is contemplated, we suggest to clarify in the guideline why biosimilars do not usually meet the conditions to be considered as a generic medicinal product (with reference to recital 15 of Directive 2004/27/EC and article 10.4 of Directive 2001/83 as amended) **Proposed change:** We suggest that the following text is considered to ensure that this definition is not confused. ‘A biosimilar is a biological medicinal product that contains an ~~a version of the~~ active substance with proven similarity ~~of~~ to that of an already authorised original biological medicinal product (reference medicinal product) ~~A biosimilar demonstrates similarity to the reference medicinal product~~ as demonstrated in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive, direct comparability exercise.’	
55	8	Comment: The draft guideline includes a definition of biosimilars which could be confused by the reader to determine that a biosimilar contains a version of the active substance of the reference medicinal product only. This is not appropriate as a biosimilar is its own product with a separate manufacturing process and different	The definition of the biosimilar product will be in line of the GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		manufacturer. Subsequent text in the guideline mentions the need for the same posology and route of administration, but without the second sentence of the definition it is open for a wider definition of biosimilars as any product with a 'similar' active substance. Formulation, route of administration, device and presentation are integral parts of a registered medicinal product and biosimilarity should be based on a comparison of the medicinal product as a whole. We therefore suggest that the definition of a biosimilar comprises both the first and the second sentence of this paragraph. Proposed change: Consider amending the text as follows: 'A biosimilar is a biological medicinal product that contains an ~~version of the~~ active substance which is highly similar to that of an already authorised original biological medicinal product (reference medicinal product) and which~~. A biosimilar~~ demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive, direct comparability exercise.'	
55-56	1	Comment: BIO suggests editing the definition offered for	The definition of the biosimilar product will be in line of the GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"biosimilar" for clarity and consistency. Proposed change: "A biosimilar is a biological medicinal product that ~~contains a version of the active substance of~~ is highly similar to an already authorised original biological medicinal product (reference medicinal product)."	
55-56	4	Comment: It is suggested that the Agency tightens the definition of a biosimilar as there seems to be a discrepancy here; if the biosimilar contains a "version" of the same active as the reference product, there could be differences in the qualitative characteristics which may or may not be reflected as clinically meaningful differences. Hence, while it is understandable that the Agency provides flexibility by use of a "version" of active in the proposed biosimilar, such a definition may lead to different conceptions.	The definition of the biosimilar product will be in line of the overarching GL for similar biological medicinal products.
55-58	2	Comment: The inclusion of the definition of a biosimilar product is highly welcomed. We also appreciate that the same wording is used as in the revised draft version of the overarching biosimilar guideline. The new wording on the definition of a biosimilar product (…contains a version of the active substance) is clear and concise and - from a scientific standpoint -	The definition of the biosimilar product will be in line of the GL for similar biological medicinal product

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the word “version” matches the inherent complexity of biological products very well and is therefore well chosen. However, we would like to draw attention to the wording used in the “EMA’s procedural advice for users of the centralised procedure for similar biological medicinal products applications (EMA/940451/2011)”, item 1: “The active substance of a similar biological product is a known biological active substance and similar to the one of the reference medicinal product.” As the biosimilar is defined by the comprehensive comparability exercise and the active substance, it is suggested that the two sentences in the definition be reversed in order. We recommend that the same expression and wording is included in the final guideline in order to ensure consistent wording across the various biosimilar guidance documents. Moreover, the consistent use of this definition will help distinguish between high-quality biosimilar products developed and licensed according to the high European standards and “non-comparable copies” of biological products available in many other parts of the world. **Proposed change:** ‘A biosimilar is a biological medicinal product that demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive	

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		comparability exercise. A biosimilar is a biological medicinal product that contains a version of a known biological active substance of an already authorised original biological medicinal product (i.e. reference medicinal product).'	
55-58	10	Comment: The new wording on the definition of a biosimilar product (…contains a version of the active substance) is clear and concise and - from a scientific standpoint - the word "version" matches the inherent complexity of biological products very well and is therefore well chosen. However, we would like to draw attention to the wording used in the "EMA's procedural advice for users of the centralised procedure for similar biological medicinal products' applications (EMA/940451/2011)", item 1: "The active substance of a similar biological product is a known biological active substance and similar to the one of the reference medicinal product." We recommend that the same expression and wording is included in the final guideline in order to ensure consistent wording across the various biosimilar guidance documents and to be consistent with the comments on line 34. Proposed change: "A biosimilar is a biological medicinal product that	The definition of the biosimilar product will be in line of the overarching GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		contains a version of a known biological active substance of an already authorised original biological medicinal product (reference medicinal product)."	
55-58	14	Comment: From the discussion at the workshop of October 31, it became clear that the definition of a biosimilar comprises both the first and the second sentence of this paragraph. This should be clarified in the guideline, to avoid that the wording opens up for a wider definition of biosimilars as any product with a similar active substance. Formulation, route of administration, device and presentation are integral parts of a registered medicinal product and biosimilarity should be based on a comparison of the medicinal product as a whole. Note: The definition should be consistent in all guidelines. Our proposal replaces our similar comment on the overarching guideline as the workshop has allowed a better understanding. It is further proposed to replace 'comprehensive by 'appropriate' as in our opinion this better reflects the case-by-case approach presented. Proposed change: A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product	The definition of the biosimilar product will be in line of the overarching GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(reference medicinal product) and has~~. A biosimilar~~ demonstrated~~s~~ similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy~~)~~ based on an appropriate ~~comprehensive~~, direct comparability exercise.	
55-58	16	Comment: Difficult to read. Maybe the brackets are misplaced. It is also not really a definition. It says that a biosimilar is a product that has been shown to be a biosimilar. Proposed change: Redefine biosimilar as a recognition by a regulatory body	The definition of the biosimilar product will be in line of the overarchingGL for similar biological medicinal products.
55-58	17	The current wording in line 55 et seq. is that '*A biosimilar is a biological medicinal product that contains a version of the active substance of an (..) reference medicinal product.*' The term 'a version of the active substance' may imply that all sorts of differences including 'significant differences' are allowable, an implication that is contrary to current practice and to the messages elsewhere in the guidance. Proposed change: A biosimilar is a biological medicinal product that contains the same or a highly similar version of the active substance of an already authorised original	The definition of the biosimilar product will be in line of the overarching GL for similar biological medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biological medicinal product (reference medicinal product).	
56	7	Proposed change: replace “original” biological medicinal product with “originator” biological medicinal product	Accepted
56-58	13	Comment: Typographical error of parenthesis Proposed change: (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.	Corrected
58	15	Comment: We suggest to modify “comparability exercise”. The concept of biosimilarity and comparability are distinct and should not be merged. Please add a reference to ensure compliance with the relevant administrative procedures and policies of the EMA and with the current guidance CHMP/437/04. Proposed change: “biosimilarity exercise”	Not accepted. The demonstration of biosimilarity relies on the experience gained in the conventional comparability exercises and is based on same scientific principles. The text will be modified in order to differentiate comparability in the context of manufacturing changes and biosimilar development.
58, 66, 144, 165, 218, 346	6	Comment: In order to differentiate the biosimilar comparability	The text will be modified in order to differentiate comparability in the context of manufacturing changes and biosimilar development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		exercise from the comparability exercise for changes introduced in the manufacturing process of a given product (i.e. changes during development and post-authorisation) as outlined by ICH Q5E, the term biosimilar comparability exercise should be used consequently in the guideline. Proposed change: […] biosimilar comparability exercise […]	
59	14	Comment: We propose to add text before line 59 to clarify that the stepwise approach applies to the entire comparative programme, from beginning to end. Proposed change: "A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data."	This GL is about (non)clinical development. It is clearly said that the (non)clinical development will normally proceed stepwise.
59-62	4	Comment: This implies that 'appropriate' but nevertheless some	No. The text is sufficient as an introduction before going into biotechnology-derived proteins. It is, however, said that the (non)clinical studies are planned on the basis of the physico-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		kind of non-clinical and clinical studies would always be required in the marketing authorization application dossier for a biosimilar product. Proposed change: It is suggested that the agency re-words the sentence to clarify the expectations.	chemical analytical studies.
60	7	Comment: add text proposed in bracket Proposed change: originator medicinal product (reference medicinal product)	Accepted
63-65	8	Comment: In line with what is mentioned in the Guideline on Quality issues (CHMP/BWP/247713/2012 – revision 1), it should be specified that although focussing on biosimilars containing recombinant DNA-derived proteins, the principles explained in the document could apply to other biosimilar products, on a case by case basis. Proposed change: Consider amending the text as follows: 'The quality issues relevant for demonstration of	The proposed text has been added to the chapter "Scope".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		comparability for biosimilars containing recombinant DNA-derived proteins are addressed in the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues (EMA/CHMP/BWP/247713/2012).* Nevertheless, the principles explained in this document could apply to other biosimilar products, on a case by case basis.'	
66-67	4	Comment: Please provide a "road map" of class specific guidances; how will the class will be selected, how will priority be established?	No. Discussion on the selection of the topics for guidelines is out of the scope. Nevertheless, a class-specific guideline is often triggered by repeated scientific advice requests concerning structurally related-products.
68	18	Introduction: Comment: It is stated that 'the nature and complexity of the reference product has an impact on the extent of the (non-) clinical studies to confirm biosimilarity'. We agree that both of these factors will have an influence on the amount of work required to confirm biosimilarity. However, we consider that another determining factor is the degree with which the reference product can be characterised in terms of its physiochemical properties at its molecular level and its mechanism of action (MoA) including the availability of suitable biomarkers. It would be useful if the definition around 'nature and	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		complexity' could be extended further to ensure that this is clear. Proposed change: Consider amending the text as follows: 'The nature and complexity of the reference product as well as the extent to which the structure and function of the reference product can be characterised has an impact on the extent of the (non-) clinical studies to confirm biosimilarity.'	
68-69	1	Comment: BIO agrees that the nature and complexity of the reference product will have an impact on the studies required to confirm biosimilarity but believes this will manifest in the ability to characterise the structure and function of the reference product. Proposed change: "The extent to which the structure and function of the reference product can be fully characterised ~~nature and complexity of the reference product~~ has an impact on the extent of the (non-) clinical studies to confirm biosimilarity."	Accepted
68-69	8	Comment: It is stated that '*the nature and complexity of the reference product has an impact on the extent of the*	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(non-) clinical studies to confirm biosimilarity'. We agree that both of these factors will have an influence on the amount of work required to confirm biosimilarity. However, we consider that the determining factors are the degree with which the reference product can be elucidated in terms of its physiochemical properties at its molecular level and its mechanism of action (MoA) including the availability of suitable biomarkers. It would be useful if the definition around 'nature and complexity' could be extended further to ensure that this is clear. Proposed change: Consider amending the text as follows: 'The extent to which the structure and function of the reference product can be characterised ~~nature and complexity of the reference product~~ has an impact on the extent of the (non-) clinical studies to confirm biosimilaity.'	
68-69	14	Comment: While it is agreed that the nature and complexity of the reference product will have an impact on the studies required to confirm biosimilarity, we consider that it is more the ability to fully characterise the structure and function of the reference product which will require more or less work necessary to confirm	Accepted, except "fully"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biosimilarity. It would be useful if the definition around 'nature and complexity' could be extended further to ensure that this is clear. Proposed change: Consider the following amended text: 'The extent to which the structure and function of the reference product can be fully characterised ~~nature and complexity of the reference product~~ has an impact on the extent of the (non-) clinical studies to confirm biosimilarity.'	
68-73	15	Comment: We propose to add the sentences in red as follows Proposed change: The nature and complexity of the reference product has an impact on the extent of the (non-)clinical studies to confirm biosimilarity. The differences observed in the physico-chemical and biological analyses will guide the planning of the (non-) clinical studies. Other factors that need to be taken into consideration are the mode of action of the active substance (e.g. receptor(s) involved) in all the licensed indications of the reference product and pathogenetic mechanisms involved in the disorders included in the therapeutic indications (e.g. mechanisms shared by	The text has been modified to include immunogenicity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		various therapeutic indications). The issue of immunogenicity must always be considered when a claim of biosimilarity is made, especially when repeated administration is proposed and when tapering interruption and retreatment, dose adjustment and similar strategies are part of the common clinical practice.	
69-70	16	Comment: In reality the differences in quality attributes between biosimilar and reference do not guide the (pre)clinical development. The outcome of the quality comparison is a yes or no answer. Yes means further confirmation of biosimilarity in (pre) clinical trials. No means the product is not a biosimilar. Proposed change: delete sentence	Not accepted. Physico-chemical and structural analysis will always reveal some differences in any new version of biotechnology derived product. It is not always possible to say simply yes/no on the basis of the current methodology and experience.
72	16	Comment: What is pathogenetic? Proposed change: Use “pathogenesis” instead of “pathogenetic pathways involved in”	No. Pathogenesis is often incompletely known.
74	8	Comment: We consider that the following text (adapted from the Guideline on Similar Biological Medicinal Products CHMP/437/04 Rev 1, 26 April 2013) should be placed before the specific discussions on non clinical and	This GL is about (non)clinical development. It is clearly said that the (non)clinical development will normally proceed stepwise. It is also said that the physico-chemical analysis will modify the following (non)clinical development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical aspects as it needs to be explained that the stepwise approach applies to the entire comparative program from the beginning of the program. Proposed change: Consider adding the following text after line 73: 'A stepwise approach is recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data.	
74	18	Introduction: Referring to 'applicants should review data from the reference product..' it should be clarified that it is a historical review of data from the literature and other documents such as EPARs. Proposed change: The applicants should review all available data from published literature and other public documents e.g. EPARs regarding the reference product on the predictive value of in vitro assays/animal models as well as correlations between dose/exposure and	It is unnecessary to define the sources of data in the GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacodynamics, on one hand, and pharmacodynamics and clinical response, on the other hand.'	
74-76	4	Comment: It is important to note that the information on the predictive value of *in vitro* assays/animal models and dose/exposure correlations may not be readily available for the reference medicinal product.	Nevertheless, the available data should be reviewed.
74-76	8	Comment: Referring to "The applicants should review data from the reference product … " it should be clarified that it is a historical review of data from the literature and other documents, such as EPARs. **Proposed change:** Consider amending the text as follows: 'The applicants should review all available data from published literature and other public documents e.g. EPARs regarding the reference product on the predictive value of *in vitro* assays/animal models as well as correlations between dose/exposure and pharmacodynamics, on one hand, and pharmacodynamics and clinical response, on the other hand.'	It is unnecessary to define the sources of data in the GL.
74-76	10	Comment: Referring to "The applicants should review data from the reference product … " it should be clarified that it is	It is unnecessary to define the sources of data in the GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a historical review of data from the literature and other documents, such as EPARs. Proposed change: "The applicants should review data from the reference product on the predictive value of in vitro assays/animal models as well as correlations between dose/exposure and pharmacodynamics, on one hand, and pharmacodynamics and clinical response, on the other hand based on information that are available in the literature and other documents such as EPARs."	
74-76	14	Comment: Referring to "The applicants should review data from the reference product … ": it could be clarified that it is a historical review of data from the literature and other documents, such as EPARs. **Proposed change:** "The applicants should review data from the reference product on the predictive value of in vitro assays/animal models as well as correlations between dose/exposure and pharmacodynamics, on one hand, and pharmacodynamics and clinical response, on the other hand based on information that is available in the literature and other documents such as EPARs."	It is unnecessary to define the sources of data in the GL.
74-76	16	Comment: Completely incomprehensible sentence	The sentence has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Rephrase in normal, understandable language	
76-77	1	**Comment:** BIO believes that the term "suitable biomarkers" should be defined with greater clarity, to include: *i.)* biomarkers used in the development of the reference product, or *ii.)* biomarkers which have a patho-physiological link to the therapeutic drug effect of the biosimilar.	No. Only the suitability for the study of biosimilarity matters.
76-77	8	Comment: Whilst we agree that the use of biomarkers may play a role during the (non-) clinical development, we nevertheless consider that an extensive *in vitro* non-clinical testing would be required during such development and any exception should be scientifically justified, and agree that they are of paramount importance for the non-clinical comparability exercise as indicated in lines 141-144. Proposed change: Consider amending the text as follow: 'Whilst the availability of suitable biomarkers may abbreviate the (non-)clinical development, a comprehensive non-clinical testing programme is expected.'	No. This is just introduction. The matter of biomarkers will be discussed in the clinical section.
76-77	10	**Comment:**	No. This is just introduction.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Referring to "The availability of suitable biomarkers …", the term "suitable biomarkers" should be defined in a clearer manner including i) biomarkers used in the development of the reference product or ii) biomarkers which have a patho-physiological link to the therapeutic drug effect of the biosimilar.	
76-77	14	Comment: As indicated in Section 4.1 lines 141-144 biomarkers are of paramount importance for the non-clinical comparability exercise. In order to be clear that a comprehensive in vitro non-clinical testing is expected during development of a biosimilar we suggest amending the text as indicated. Proposed change: Whilst the availability of suitable biomarkers may abbreviate the (non-)clinical development, a comprehensive ***in vitro*** non-clinical testing programme is expected during such development.	It is not possible all deal with all matters of the guideline already in the introduction.
77-78	1	Comment: While BIO agrees that the safety profile of the reference product is very important and informative in determining the focus of safety studies, BIO believes that safety studies should also be informed by residual uncertainty remaining from the analytical, early-clinical and clinical biosimilarity assessment.	It is expected that the biosimilars will have the same safety issues as the reference product. Nevertheless, "mainly" (determine) was added. Immunogenicity has to be addressed always pre-licensing. The need for post-licensing studies depends on the experience from the reference product and the outcome of the comparative immunogenicity studies. In general, immunogenicity studies will be required. However,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		BIO also believes that it is important for immunogenicity studies to be conducted pre- and post-authorisation regardless of the immunogenic profile of the reference product. Proposed change: "The safety profile of the reference product will ~~determine~~ inform the focus of the safety studies both pre- and post-marketing. However, immunogenicity studies will always be required."	in specific cases deviation from this approach might be acceptable.
77-78	8	Comment: While we agree that the safety profile of the reference product is very important and informative in determining the focus of safety studies and immunogenicity profile pre- and post-marketing, we consider that safety and immunogenicity studies should also be informed by residual uncertainty remaining from the analytical, early-clinical and clinical biosimilarity assessment. In addition it should be clear that in all instances immunogenicity studies will be required. Proposed change: Consider amending the text as follows: 'The safety profile of the reference product and the data generated during development of the biosimilar will ~~determine~~ inform the focus of the safety studies both	Not accepted. It is expected that the biosimilars will have the same safety issues as the reference product. Nevertheless, "mainly" (determine) was added. Immunogenicity has to be addressed always pre-licensing. The need for post-licensing studies depends on the experience from the reference product and the outcome of the comparative immunogenicity studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pre- and post-marketing. Immunogenicity studies will be required.'	
77-78	13	Comment: On lines 77 and 78 of the draft guideline revision the reader is recommended to refer to the safety profile of the reference product to determine the focus of the safety studies required both pre- and post-marketing. We would suggest clarifying if this refers to both non-clinical and clinical safety studies and have suggested a small amendment to the wording below to clarify this. Proposed change: The safety profile of the reference product will determine the focus of the non-clinical and/or clinical safety studies both pre- and post-marketing.	The text has been modified.
77-78	14	Comment: While we agree that the safety profile of the reference product is very important and informative in determining the focus of safety studies, we consider that safety studies should also be informed by residual uncertainty remaining from the analytical, early-clinical and clinical biosimilarity assessment and the subsequent discussion on the limitations of these data (in accordance with the requirements for the Risk Management Plan).	Not accepted. It is expected that the biosimilars will have the same safety issues as the reference product. Nevertheless, "mainly" (determine) was added. Immunogenicity has to be addressed always pre-licensing. The need for post-licensing studies depends on the experience from the reference product and the outcome of the comparative immunogenicity studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We also consider that it is important for immunogenicity studies to be considered pre- and post authorisation regardless of the immunogenic profile of the reference product. Proposed change: "The safety profile of the reference product and the data generated during development of the biosimilar (bearing in mind the limitations of such data) will inform the focus of safety studies (including immunogenicity studies) both pre- and post-marketing"	
77-78	15	Comment: We suggest to add the sentences in red as follows Proposed change: The safety profile of the reference product will determine the focus of the safety studies both pre- and post-marketing. The extent of immunogenicity studies will depend on the nature of the product, the patient population and the possible consequences, dose and frequency of admnistration'	No. It not necessary to distinguish immunogenicity from safety in the introduction.
77-78	16	Comment: What is meant by the "focus"? The focus is always showing similarity. And if the product is biosimilar the safety can be assumed to be the same as the reference. Proposed change: delete sentence	No. The safety profile of the reference product will certainly shape the pre-licensing comparative studies as well as the special safety studies post-licensing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
80-82	2	Comment: It is appreciated that the biosimilar applicants have to design and, if applicable, fine-tune their non-clinical and clinical development plans based on the results of the preceding physico-chemical and in vitro biological/functional analysis of the biosimilar and the reference products. The degree of physico-chemical and biological comparability achieved in the early parts of the biosimilar development should determine the amount of further studies to be conducted. Where a biosimilar product has been shown to have appropriate similarity to the reference product supported by the comprehensive physico-chemical and functional analysis, it may allow for a very tailored non-clinical and clinical development which may be very different and less comprehensive between various applicants on a case-by-case basis.	Agree on fine- tuning but main driver of the pre- and post-licensing safety studies is the experience from the reference product.
80-82	4	Comment: This implies that it is okay for the applicants to continue to do so (i.e. fine tune their (non-)clinical studies according to the results of preceding physico-chemical and in vitro biological analyses of the biosimilar and the reference product) based on the product specific data. Is there an expectation from the Agency that such 'fine tuning', if done, should be discussed with the Agency during the biosimilar development? If yes, please clarify.	The nature of and experience from the reference product will mainly drive the (non)clinical program. Fine tuning means additional tests to clarify uncertainties derived from the physico-chemical and structural analysis. If the Applicant will not perform tests recommended in the GL, it is expected to consult the regulatory authorities in advance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
80-82	10	Comment: It is appreciated that the biosimilar applicants have to design and, if applicable, fine-tune their (non-)clinical development plans based on the results of the preceding physico-chemical and *in vitro* biological analysis of the biosimilar and the reference product. The degree of physico-chemical and biological comparability achieved in the early parts of the biosimilar development should determine the amount of further studies to be conducted. Depending on the biosimilarity demonstrated for a certain biosimilar product, the guideline allows for a tailored (non-)clinical development which may differ between various applicants e.g. with regards to the size of the (non-)clinical studies needed.	The nature of and experience from the reference product will mainly drive the (non)clinical program. Fine tuning means additional tests to clarify uncertainties derived from the physico-chemical and structural analysis. If the Applicant will not perform tests recommended in the GL, it is expected to consult the regulatory authorities in advance.
80-82	16	Comment: See also comments at lines 69-70. Clinical trials cannot be fine-tuned on the basis of quality attributes. If we would know the clinical consequences of quality characteristics we would not need a biosimilar regulatory pathway. Proposed change: delete sentence	No. The concept of stepwise development means that previous steps may have an impact on subsequent steps. This concept has being applied in the development of current biosimilars and in the development plans of biosimilar candidates. For example, some differences in the glycosylation pattern may trigger special non-clinical *in vitro* functional test.
84-86	14	Comment: We propose to add under scope some wording which explains what is intended to be covered by the	No. The scope is accurate as it is. The hierarchy of guidelines is clear. Product-specific GLs are mentioned in the introduction.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		overarching guideline and how the overarching guideline relates to the analogous general guidance on preclinical and clinical aspects as well as class specific guidelines such as for biosimilar monoclonal antibodies. The guidances should make clear when requirements are targeted for smaller/simpler biotech products only and when reference is made to high level principles applicable to all biotech proteins. Proposed change: '…. of biosimilars containing recombinant proteins as active substance(s). It addresses high level principles which are applicable to all biosimilars containing biotechnology-derived proteins, regardless of their complexity. For further guidance on specific classes of biosimilars, please refer to the relevant class-specific guidance. This guideline does not address…..”	
84-88	17	Comment: According to the title, this GL apparently concerns similar biological medicinal products containing biotechnology-derived proteins. However, in the scope this appears to be limited to recombinant proteins. Definitions in different GLs on biotechnology-derived proteins or biotechnological products vary al little between GLs. Generally descriptions are similar, but some are more or less precise. We prefer the slightly more extensive and precise	“Recombinant” is replaced by “biotechnology-derived. The possibility to apply the same principles to other proteins is also mentioned.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		wording provided in the scope of ICH Topic Q 5 E Comparability of Biotechnological/Biological Products (CPMP/ICH/5721/03). Proposed change: This guideline addresses the general principles for the non-clinical and clinical development and assessment of the marketing authorisation applications of biosimilars containing ~~recombinant~~ proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures. The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the Agency to determine applicability. ~~as active substance(s).~~ This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e. changes during development and post-authorisation).	
84-88	18	Scope:	The hierarchy of the GLs in mentioned in the introduction.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This guideline needs to have some context added here indicating what is intended to be covered here compared to the overarching guideline as well as the analogous guidance on preclinical and clinical aspects of class specific guidelines such as biosimilar monoclonal antibodies. MAbs are also biotech proteins so is this guidance intended to cover only high level principles applicable to all biotech proteins or is it intended to be more targeted for smaller biotech proteins? We believe that this guidance applies to all biosimilars containing biotechnology-derived proteins, regardless of their complexity and if this is the case we believe that this should be explicitly stated. We recommend that the context is clarified and the content is adjusted accordingly. Proposed text: Under the Scope heading, we propose to add the following text to line 86 after the first sentence: 'This guideline addresses the high level principles which are applicable to all biosimilars containing biotechnology-derived proteins, regardless of their complexity. For further guidance on specific classes of biosimilars refer to the relevant class specific guidance.'	
84-88	20	Comment: ("This guideline does not address the comparability	This issue is covered in the corresponding quality GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		exercise for changes introduced in the manufacturing process of a given product (e.g., changes during development and post-authorisation).")<u></u>: We agree with that this guideline should not apply to manufacturing changes made by a single manufacturer. Generally more data and information will be needed to establish biosimilarity of products made by different companies than would be needed to establish that one company's post-manufacturing change product is comparable to its pre-manufacturing change product. We suggest, however, that the final guideline note that the same comparability exercise for manufacturing changes will be required for biosimilar products as for originator products.	
86-88	2	Comment: It is stated that the guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product. While this is acknowledged, we would like to draw the CHMP's attention to the fact that in the current revised version of the overarching biosimilar guideline it is written that "the scientific principles of such a biosimilar comparability exercise are based on those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E)". This statement is in line with the current thinking of the EU regulators who have repeatedly stated in publications and	This issue is covered in the corresponding quality GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		presentations given at conferences that the scientific principles of the comparability/biosimilarity exercise between a biosimilar and a reference product and the comparability after manufacturing changes are based on the same scientific approach. Therefore, we suggest including the same wording as proposed in the draft version of the overarching biosimilar guideline. **Proposed change:** This guideline does not explicitly address the comparability exercise for changes introduced in the manufacturing process of a given product, however it should be considered that the scientific principles of a biosimilar comparability exercise are based on those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E).	
86-88	4	Comment: To avoid confusion, it might be worthwhile for the Agency to consider an approach similar to the FDA's where the term 'comparability' is encouraged to be used *only* in the context of manufacturing process changes. Whereas the term 'similarity' is only used when speaking of any comparability/biosimilarity of the proposed biosimilar to the reference medicinal product.	No. While it is important to avoid confusion of the type of comparability in the text, the scientific principles are the same in both scenarios.
86-88	10	Comment:	No. The corresponding quality GL will deal with this issue.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is stated that the guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product. While this is acknlowledged, we would like to draw your attention to the fact that on the current revised version of the overarching biosimilar guideline it is written that “the scientific principles of such a biosimilar comparability exercise are based on those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E)”. This statement is in line with the current thinking of the EU regulators who have repeatedly stated in publications and presentations given at conferences that the scientific principles of the comparability/biosimilarity exercise between a biosimilar and a reference product and the comparability after manufacturing changes are based on the same scientific approach. Therefore, we suggest to include the same wording as proposed in the draft version of the overarching biosimilar guideline. Proposed change: “This guideline does not explicitely address the comparability exercise for changes introduced in the manufacturing process of a given product, however it should be considered that the scientific principles of such a biosimilar comparability exercise are based on those	

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		applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E)".	
90-114	8	Comment: This section should be deleted as has been recommended for more updated guidance documents. The legal basis is clear on the EMA website advice for applicants and the list of guidance documents rapidly becomes outdated. In addition there is no distinction made between specific biosimilars guidance which is directly applicable and other guidances which are partially applicable at best. Proposed change: This section should be replaced with a reference to the EMA website guidance section for biosimilars which clearly lays out the guidance to be considered specifically on biosimilars and more peripherally on more general guidance.	The list of relevant GLs is added to all CHMP GLs.
90/114	14	Comment: This section should be deleted as has been recommended for more recently updated guidance documents. The legal basis is clear on the EMA website advice for applicants and the list of guidance documents rapidly becomes outdated. Proposed change:	The list of relevant GLs is added to all CHMP GLs.

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		This section should be replaced by a reference to the EMA website guidance section for biosimilars, which clearly lays out the guidance to be considered specifically on biosimilars and the more peripherally relevant general guidance.	
90-114	18	Legal basis and relevant guidelines: This section should be deleted as has been recommended for more recently updated guidance documents. The legal basis is clear on the EMA website advice for applicants and the list of guidance documents rapidly becomes updated. In addition there is no distinction made between specific biosimilars guidance which is directly applicable and other guidances which are partially applicable at best. This should be replaced with a reference to the EMA website guidance section for biosimilars which clearly lays out the guidance to be considered specifically on biosimilars and more peripherally on more general guidance.	The list of relevant GLs is added to all CHMP GLs.
90-91	19	Proposed change: Directive 2001/83/EC, as amended in particular ~~in Directive 2001/83/EC~~ Art 10(4) and Part II of the Annex I ~~of Directive 2001/83/EC, as amended~~.	The text has been modified accordingly.
114	18	We believe that the following text (taken from the overarching guideline) should be placed before the specific discussions on non clinical and clinical aspects as it needs to be explained that the stepwise approach	No. This is (non)clinical GL. The overarching GL for similar biological medicinal products will define the stepwise development process.

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		applies to the entire comparative program from the beginning of the program. A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data.	
115-118	11	Comment: *4. Non clinical studies* *Non-clinical studies should be performed before initiating clinical trials. A step-wise approach should be applied to evaluate the similarity of biosimilar and reference product. In vitro studies should be conducted first and a decision then made as the extent, of what, if any, in vivo work will be required.* The value of analytical studies should be made clear here to set up for Step 1. Proposed change: *4. Non clinical studies*	Partly agreed. The value of analytical and *in vitro* non-clinical studies is stressed in the revised GL version. *Proposed change - Agreed, in modified form* Analytical studies (see *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues;* EMA/CHMP/BWP/247713/2012) and *in vitro* pharmacological/ toxicological studies should be conducted first and a

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		Non-clinical studies should be performed before initiating clinical trials. A step-wise approach should be applied to evaluate the similarity of biosimilar and reference product. ***Analytical studies to determine extent of similarity should be conducted first, followed by*** *in vitro studies* ***if necessary*** ~~*should be conducted first*~~ *and a decision then made as the extent, of what, if any, in vivo work will be required.*	decision then be made as the extent, of what, if any, *in vivo* work will be required.
116	1	Comment: In line with the step-wise approach recommended by the CHMP for the development of biosimilar products, BIO believes that the guideline should require non-clinical studies to be conducted prior to clinical development. Proposed change: "Any ~~N~~non-clinical studies will ~~should~~ be performed before initiating clinical trials."	Not agreed. The current text is clear enough. The step-wise conduct of non-clinical and clinical studies is mentioned. It is agreed that non-clinical studies should be performed prior to clinical development. However, additional non-clinical studies may also be required to support the later stages of clinical development, as to be justified by the Applicant on a case-by-case basis.
116-117	8	Comment: This section is similar to the MAbs guidance – should this be identical or is it intended to be an overview? If it is intended to be an overview this should be stated upfront. If there are differences which are supposed to be applicable to smaller biotech proteins this should be made clear upfront. Additionally, in line with the step-	Not agreed. (i) This GL lays down the general principles for non-clinical and clinical evaluation of biosimilar medicinal products containing biotechnology-derived proteins as active substance. As such, it is principally applicable to complex as well as structurally more simple products. Nevertheless, in line with the described step-wise approach, the specific

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		wise approach recommended by the CHMP for the development of biosimilar products, we consider that non-clinical studies will be conducted prior to clinical development. Also, in the current guideline it is stated that the non-clinical studies should be comparative in nature and should be designed to detect differences in response between the similar biological product and the reference medicinal product and not just the response *per se*. As this covers both *in* vitro and *in vivo* studies, this important clarification should be kept in the revised guideline. Proposed change: Consider amending the text as follows: 'Non-clinical studies ~~should~~ will be performed before initating clinical trials, unless justified. These studies should be comparative in nature and should be designed to detect differences in response between the similar biological product and the reference medicinal product and not just the response ***per se***.'	evaluation has to be adjusted on a case-by-case basis, taking into account all available data. *(ii) Proposed change – Not agreed.* It is agreed that the non-clinical studies should usually be comparative in nature. In line with this, the recommendation that non-clinical *in vitro* studies should generally follow such an approach is already contained in GL section 4.1. However, there may be situations where non-clinical (*in vivo*) studies may rather be performed in a non-comparative than in a strictly comparative way, e.g. to take into account the 3R principles. Therefore, it is preferred not to include an additional reference to the "comparative" principle in the introductory paragraph.
116-118	2	**Comment:** **Comment:** The step-wise approach for the conduct of non-clinical	Comments are acknowledged.

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		studies as proposed in this revised draft version of the guideline is very much appreciated and is in line with the high scientific principles of the current thinking of biosimilar product development as conveyed by the European regulators. In addition, it is expected that only the relevant non-clinical studies need to be performed to support comparability and safety before initiating clinical trial applications. **Proposed change:** Relevant non-clinical studies to support comparability and safety should be performed before initiating clinical trials.	*Proposed change – Agreed, with slight modification* To support biosimilarity, relevant non-clinical studies should be performed before initiating clinical trials.
116-118	10	Comment: The step-wise approach for the conduct of non-clinical studies as proposed in this revised draft version of the guideline is appreciated. This is line with the high scientific principles of the current thinking of biosimilar product development as conveyed by the European regulators. Accordingly, we agree that there may be situations whereby *in vivo* non-clinical studies may not be needed.	Comments are acknowledged.
116-118	14	Comment: The step-wise approach for the conduct of non-clinical	Comments are acknowledged .

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		studies as proposed in this revised draft version of the guideline is appreciated. This is in line with the high scientific principles of the current thinking of biosimilar product development as conveyed by the European regulators. Accordingly, we agree that there may be situations whereby *in vivo* non-clinical studies may not be needed. It would be inherent to such a stepwise approach that non-clinical studies have to be conducted prior to clinical development. It is noted that this overview is very similar to the overview given in the specific mAbs guidance. In the guideline hierarchy this is confusing because class specific guidance is expected to address class-specific approaches. If there are differences, it would be helpful to indicate these clearly upfront. Proposed change: 'Non-clinical studies will ~~should~~ be performed before initiating clinical trials.'	See comment on stakeholder 8, lines 116-117. *Proposed change - Not accepted .* It is preferred to keep the current wording, which is more in line with the step-wise, case-by-case approach of the GL.
116-122	16	Comment: completely self-evident. This type of "guidance" does not belong in a scientific guideline. Proposed change: delete	Not agreed. The fact that several comments have been received for the introductory paragraph shows that, obviously, the content is not self-evident.
116-124	18	Non-clinical studies:	See comments on stakeholder 8, lines 116-117.

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		As per earlier comment – this is similar to the MAbs guidance – should this be identical or is it intended to be an overview? If it's intended to be an overview this should be stated upfront. If there are differences which are supposed to be applicable to smaller biotech proteins this should be made clear upfront	
117-118	4	Comment: Since assessment of toxicity is not completely possible *in vitro*, could the Agency provide clarification with a step-wise approach for the assessment of pharmacodynamics, toxicokinetics, local tolerance, and toxicity.	Comments are acknowledged. The principles for the step-wise evaluation of the non-clinical pharmacodynamic, toxicokinetic and toxicological properties of the claimed biosimilar product are laid down in the non-clinical section of this GL
117-118	8	Comment: Safety signals or changes in PK/PD can be screened for in limited *in vivo* studies in relevant animal models before subjecting clinical subjects to unknown risk factors. This should be noted in the revised guideline. It should be determined by the sponsor, on a case-by-case basis what the scope of this testing should be to adequately determine the safety profile of the investigational product. It should also be borne-in-mind that by the time the application is submitted there is clinical data so the in vivo data would never be needed, and skipping that step is on the company's decision since there is no regulatory review for this other than the CTA process for each individual country. This should be considered by the Agency further when	Not agreed.

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		discussing a stepwise approach. Proposed change: Consider amending the text as follows: '*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. As biotechnology-derived proteins may mediate ***in vivo*** effects that cannot be fully elucidated by ***in vitro*** data, a justification for not conducting ***in vivo*** studies should be provided (refer to Section 4.2 below).'	*Proposed change – Not agreed.* The fact that biotechnology-derived proteins may mediate in vivo effects that cannot be fully elucidated by in vitro data is already contained in the GL (section 4.2) and does not need to be repeated here upfront. As indicated in section 4.2, if the quality biosimilar comparability exercise and the *in vitro* non-clinical studies are considered satisfactory and no issues are identified which would block direct entrance into humans, *in vivo* animal studies are usually not required and further specific justification is not considered necessary in such a case.
119-122	11	Comment: *It is important to note that design of an appropriate non-clinical study program requires a clear understanding of the reference product characteristics. Results from the physical-chemical and biological characterisation studies (i.e. comparability of the biosimilar to the reference product (should be reviewed from the point of view of potential impact on efficacy and safety.* This small paragraph should be expanded into a new Step 1 as outlined in General Comments. Proposed change: Step 1. Analytical studies *It is important to note that design of an appropriate*	Not agreed. *Proposed change – Not agreed* The proposed wording is considered as to detailed for this general GL. Furthermore, the mentioned issues are better suited

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		non-clinical study program requires a clear understanding of the reference product characteristics. Results from the physical-chemical and biological characterisation studies (i.e. comparability of the biosimilar to the reference product (should be reviewed from the point of view of potential impact on efficacy and safety. Firstly, an analysis of the difference in manufacturing changes should be made with a view to determining if these are likely to result in any biologically relevant changes. Secondly, analytical techniques should be used to determine the extent of similarity with the reference product. Techniques include mass spectrometry, x-ray crystallography, protein labelling methods (e.g. HDX-MS) and nuclear magnetic resonance.	for/discussed in the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues* (EMA/CHMP/ BWP/247713/2012).
119-122	15	Comment: We suggest editing the text for clarity Proposed change: "It is important to note that design of an appropriate non-clinical study program requires a clear understanding of the reference product characteristics. It also must consider the results from the physico-chemical and biological characterisation studies (i.e. comparability of the biosimilar to the reference product) from the point-of-view of potential impact on efficacy and safety	Not agreed. *Proposed change – Not agreed* The step-wise approach for non-clinical development of biosimilars is based on a case-by-case evaluation of the available data. To reflect this, the current wording ("should be considered") is preferred.

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123-124	10	Comment: We agree that the approach to non-clinical studies should be flexible and tailored to the product concerned on a case-by-case basis.	Comments are acknowledged.
125	17	Comment: We do not see that the non-clinical development is really stepwise. The mainstay is *in vitro* studies, and only in exceptional cases an animal study could be anticipated. The second step (Determination of the need for *in vivo* studies) is not really a step and the relevant discussion can be included in the paragraph on *in vivo* studies. Proposed change: 4.1. ~~Step 1:~~ *In vitro* studies	Not agreed. *Proposed change – Not agreed* It is agreed that a rearrangement of the text as proposed by stakeholder 17, would indeed be possible. However, since the current wording emphasizes the basic principle of the step-wise approach more clearly, it is preferred.
126-128	4	Comment: If the data from some of the quality-related assays is to be provided in the non-clinical assessment, where should these specific *in vitro* study reports be included, in Module 4 or Module 3? Additionally, if *in vivo* studies such as xenograft type/tumor regression studies are performed to support the analytical similarity and to define the critical quality attributes for the product - where should such studies reside? Would it be buried somewhere under Section 32R in Module 3 (where the	Assays which belong to the quality-related part of the biosimilar comparability exercise should normally be documented in module 3. On the other hand, additional non-clinical *in vitro* studies and/or *in vivo* animal studies should usually be documented in module 4.

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		biosimilarity results are presented), or under the 'other toxicity studies' (Section 4.2.3.7.7) of Module 4? Such clarifications are essential for the applicant to provide a complete and accurate dossier.	
129	8	Comment: It is suggested to modify the text to ensure that in order to generate reliable data qualified assays should be used. Proposed change: Consider amending the text as follows: 'These studies could include qualified relevant assays on : …'	Not agreed. There is no commonly accepted definition for "qualified assay" in the scientific literature.
129	13	Comment: In vitro comparative studies addressing target binding and signal transduction and functional activity/viability are an integral part of comparability, thus we propose a stronger emphasis on this requirement. Proposed change: These studies should include relevant assays on:	Comments are acknowledged. *Proposed change - Accepted in slightly modified form* These studies should usually include relevant assays on:
129-133	8	Comment: References to recommended studies for target binding, signal transduction, and cellular activity/viability	Not agreed. The non-clinical biosimilar comparability exercise is based on a comprehensive analytical comparison of the

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		restrict these to those targets or activities known to be of relevance for the pharmaco-toxicological effects of the reference product. These restrictions omit the possibility for unknown or enhanced activities that may be mediated by targets or cells known to interact with the product. For example, IgGs can bind to Fc receptors with varying affinities, and even if such interactions are not associated with the primary mechanism of action, the relevance of these to the pharmaco-toxicological effects may not be known. A significant change in binding activity to such receptors should be ruled out or otherwise justified for the biosimilar product. Furthermore, the binding of a biosimilar product candidate to a related (off-target) species could differ from that of the reference product, and it may therefore be relevant to confirm similar binding specificity. Proposed change: Consider the following amended text: '- *Binding* to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects of the reference product, or that are otherwise likely to bind to the reference product with relevant affinities.	physicochemical and biological properties of the claimed biosimilar and the chosen reference product, complemented by a comprehensive comparison of the spectrum of pharmaco-toxicological effects known to be of relevance for the reference product in appropriate *in vitro* assays (step 1 of the non-clinical evaluation). If these data are considered satisfactory and no issues are identified which would block direct entrance into humans, additional ´off-target` *in vitro* studies, as requested by stakeholder 8, are not expected to reveal unknown or enhanced activities. The request by stakeholder 8 for non-clinical evaluation of IgGs, i.e. to perform Fc-receptor binding/activity studies is covered by the existing GLs as such studies are explicitly mentioned in the monoclonal biosimilar GL.

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		- *Signal transduction and functional activity/viability* of cells known to be of relevance for the pharmaco-toxicological effects of the reference product or for which an unexpected increase in activity could be relevant to the pharmaco-toxicological effects of the biosimilar product (eg, effector function for mAbs).'	
129-133	14	Comment: References to recommended studies for target binding, signal transduction, and cellular activity/viability restrict these to those targets or activities known to be of relevance for the pharmaco-toxicological effects of the reference product. These restrictions omit the possibility for unknown or enhanced activities that may be mediated by targets or cells known to interact with the product. For example, IgGs can bind to Fc receptors with varying affinities, and even if such interactions are not associated with the primary mechanism of action, the relevance of these to the pharmaco-toxicological effects may not be known. A significant change in binding activity to such receptors should be ruled out or otherwise justified for the biosimilar product. Furthermore, the binding of a biosimilar product candidate to a related (off-target) species could differ from that of the reference product, and it may therefore be relevant to confirm similar binding specificity.	Not agreed. See comment on stakeholder 8, lines 129-133.

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		Proposed change: Consider the following amended text: 'These studies could include relevant assays on: - Binding to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects of the reference product, or that are otherwise likely to bind to the reference product with relevant affinities. - Signal transduction and functional activity/viability of cells known to be of relevance for the pharmaco-toxicological effects of the reference product or for which an unexpected increase in activity could be relevant to the pharmaco-toxicological effects of the biosimilar product (eg, effector function for mAbs).'	
130-131	7	Comment: Note that binding to target would need to be established not only in human but also in animal species to support the toxicology program. This is implies in line 140, but should be stated explicitly. Proposed change: The guideline might also want to specify receptors, such as FcRn, which are important for PK of mAbs	Comments are acknowledged. *Proposed change – Agreed, in modified form* Binding to target(s) (e.g. receptors, antigens, enzymes) known to be involved in the pharmaco-toxicological effects and/or pharmacokinetics of the reference product.
132	7	Comment:	Not agreed.

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		Specify that the in-vitro potency assay needs to be conducted for both the biosimilar and the reference product.	The GL text already indicates that data from a number of "comparative" *in vitro* assays should usually be provided
132-133	5	Comment: In the guideline, "parameters sensitive enough to detect differences" is emphasized for comparability study. Signal transduction is evaluated by changes in biomarkers in signal pathway. The results are shown by western blot analysis, which is more qualitative than quantitative, in general. For this reason, the result of signal transduction is not considered to be "sensitive enough to detect differences" for comparability assessments and therefore its value needs to be reconsidered.	Not agreed. Western blot analysis is just one possibility to evaluate biosimilarity. On a case-by-case basis, other parameters (e.g. formation of second messengers such as cAMP, cGMP, inositol phosphates etc.) may be investigated for which, usually, sensitive assays are available to detect potential clinically relevant differences between the reference product and the claimed biosimilar.
134-135	2	Comment: It is acknowledged that in vitro assays of the non-clinical comparability should be sensitive enough to detect potential differences with clinical relevance. **Proposed change:** The studies should evaluate parameters sensitive enough to detect differences with clinical relevance.	Agreed. *Proposed change – Agreed, in slightly modified form* The studies should evaluate parameters sensitive enough to detect differences with potential clinical relevance.
134-135	16	Comment: what is the meaning of : parameters sensitive enough to find differences? In principle parameters can be chosen and assays can be made sensitive enough to find differences even between vials of the same product. And should not also be different batches of	Agreed, in modified form. See also comment on stakeholder 2, lines 134-135. As indicated above, the studies should evaluate parameters sensitive enough to detect differences with potential clinical relevance. It is agreed that it is reassuring for the biosimilar

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		the reference product be compared? Should the parameters not be restricted to those normally used to characterize the products and the difference between biosimilar and reference not be greater than the variation seen between different batches of the reference? Proposed change: rethink the approach and make it more scientifically sound.	comparability exercise if the difference between biosimilar and reference product is not greater than the variation seen between different batches of the reference product.
137-137	17	Comment: Several requirements for the non-clinical *in vitro* studies are described here. In order for the results being conclusive these should be unambiguous. There we propose an additional sentence after the first. Proposed change: The studies should be comparative in nature and should not just assess the response per se. *To obtain unambiguous results, the methods used should be scientifically valid and suitable for their purpose.*	Agreed. *Proposed change – Agreed.* The studies should be comparative in nature and should not just assess the response per se. To obtain unambiguous results, the methods used should be scientifically valid and suitable for their purpose.
135-137	6	Comment: It is recommended to revise the wording to comply with the most recent version of the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical*	Not agreed. See comment on stakeholder 17, lines 135-137, below

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		issues). Proposed change: The studies should assess the concentration–activity/binding relationship between the biosimilar and the reference medicinal product covering a concentration range which is sensitive enough to detect differences.	
135-137	17	Comment: "*The studies should assess the concentration–activity/binding relationship between the biosimilar and the reference medicinal*" This needs to be rephrased. It is not the relationship between biosimilar and reference product that needs to be assessed. Proposed change: The studies should <u>compare the biosimilar and the reference medicinal product for</u> ~~assess~~ the concentration–activity/binding relationship between <u>the product and the pharmacological target</u> covering a concentration range where differences are most sensitively detected.	Agreed, in modified form. It is agreed that the sentence needs to be rephrased (see below). *Proposed change – Agreed in modified form* The studies should compare the concentration–activity/binding relationship of the biosimilar and the reference medicinal product at the pharmacological target, covering a concentration range where differences are most sensitively detected.
137-139	1	Comment: BIO suggests providing a recommendation regarding the characteristics of the lots of reference product for	Agreed.

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		in vitro biosimilarity testing. Proposed change: "They should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of that in clinical use and intended for clinical use, respectively."	*Proposed change – Agreed* They should be performed with an appropriate number of batches of the reference product and of the biosimilar product, representative of that in clinical use and intended for clinical use, respectively.
137-139	4	Comment: A clarification on the number of batches that are considered 'appropriate' by the Agency would be helpful for applicants.	See comment on stakeholder 17, line 138.
137-139	8	Comment: No recommendation is provided regarding the characteristics of the lots for the reference product for the in vitro comparability testing. Proposed change: Consider amending the text as follows: 'They should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of that in clinical use and intended for clinical use, respectively.'	Agreed. See comment on stakeholder 1, lines 137-139.
137-139	13	Comment: Line 137-139 states that in vitro studies "… should be performed with an appropriate number of batches of product representative of that intended for clinical	See comment on stakeholder 17, line 138.

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		use." It would be useful to Sponsor's to include some further information in order to help explain how the EMA determines whether the number of batches of product tested is appropriate.	
137-139	14	Comment: No recommendation is provided regarding the characteristics of the lots for the reference product for the in vitro comparability testing. Proposed change: "They should be performed with an appropriate number of batches of the reference product representative of that authorised in the EEA and of the biosimilar intended for clinical use."	See comment on stakeholder 1, lines 137-139. Under certain conditions (see revised GL text) batches of the reference product produced outside of the EEA may be used. *Proposed change – Partly agreed* They should be performed with an appropriate number of batches of the reference product and of the biosimilar product, representative of that in clinical use and intended for clinical use, respectively.
137-139	15	Comment: No recommendation is provided regarding the characteristics of the lots for the reference product for the in vitro comparability testing. Proposed change: "They should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of that in clinical use and intended for clinical use, respectively."	See comment on stakeholder 1, lines 137-139.
137-139	18	Comment: No recommendation is provided regarding the	See comment on stakeholder 14, lines 137-139.

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		characteristics of the lots for the reference product for the in vitro comparability testing. Proposed change: "They should be performed with an appropriate number of batches of the reference product representative of that authorised in the EEA and of the biosimilar intended for clinical use."	
138	17	Comment: The question how much is an appropriate number of batches is often posed. We propose to add a sentence for clarification. Proposed change: We propose to add a sentence similar to: "Assay and batch-to-batch variability will affect the number needed. The number tested should be sufficient to draw meaningful conclusions on the range of values of a certain parameter in both biosimilar and reference product and on the similarity of both products."	Agreed. *Proposed change - Agreed* Assay and batch-to-batch variability will affect the number needed. The number tested should be sufficient to draw meaningful conclusions on the range of values of a certain parameter in both biosimilar and reference product and on the similarity of both products.
140	17	Comment: The wording "Together these assays should broadly cover the spectrum of…." is too open and permits the omission of relevant assays. Proposed change: *"Together these assays should ~~broadly~~ cover the*	Agreed. *Proposed change - Agreed* Together these assays should cover the whole spectrum of pharmacological/ toxicological aspects known to be

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		whole *spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class."*	of clinical relevance for the reference product and for the product class.
140-141	1	Comment: BIO appreciates the emphasis on the importance of the *in vitro* non-clinical studies and the fact that these are considered paramount for the non-clinical comparability exercise. BIO believes that these studies should use test systems that are reflective of the underlying disease etiology. Also, BIO recommends specifically mentioning that studies should assess clinically relevant aspects secondary to the primary target. Proposed change: "Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class, using test systems that are reflective of the underlying disease etiology and current scientific knowledge. Studies should include the assessment of pharmacological/toxicological aspects known to be clinically important but secondary to the primary target (*e.g.*, multiple clinically active cytokines may be affected indirectly through the activity of a single cytokine agonist or antagonist)."	Partly agreed. It is agreed that the used test systems should be reflective of the current scientific knowledge and preferably include, if available, test systems that are reflective of the underlying disease etiology. The revised GL contains the following wording in section 4.1: The Applicant should justify that the *in vitro* assays used are predictive for the human *in vivo* situation according to current scientific knowledge. Together these assays should cover the whole spectrum of pharmacological/ toxicological aspects known to be of relevance for the reference product and for the product class. Therefore, the GL text covers the proposal by stakeholder 1, that ´Studies should include the assessment of pharmacological/toxicological aspects known to be clinically important but secondary to the primary target.`

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140-141	15	Comment: Draft guidance reads “Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class.” Proposed change: We suggest to modify the sentence as follows “Studies should include the assessment of pharmacological / toxicological aspects known to be clinically important but secondary to the primary target. For example, multiple clinically active cytokines may be affected indirectly through the activity of a single cytokine agonist or antagonist”.	See comment on stakeholder 1, lines 140-141.
140-144	8	Comment: We appreciate the emphasis on the importance of the *in vitro* non-clinical studies and the fact that these are considered paramount for the non-clinical biosimilarity exercise. We strongly support the notion that there are situations, based on their superior specificity and sensitivity to detect changes, whereby *in vitro* studies may be more sensitive to assessing the potential functional consequences of potentially observed differences between the biosimilar and the reference product than *in vivo* studies. These studies should use	See comment on stakeholder 1, lines 140-141.

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		test systems that are reflective of the underlying disease aetiologies. Proposed change: Consider amending the text as follows: 'Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class, using test systems that are reflective of the underlying disease etymologies and current scientific knowledge. Studies should include the assessment of pharmacological / toxicological aspects known to be clinically important but secondary to the primary target. For example, multiple clinically active cytokines may be affected indirectly through the activity of a single cytokine agonist or antagonist.'	
140-144	10	Comment: We appreciate the emphasis on the importance of the in vitro non-clinical studies and the fact that these are considered paramount for the non-clinical comparability exercise . We strongly support the notion that, based on their superior specificity and sensitivity to detect changes, in vitro studies are generally more sensitive to assessing the potential functional consequences of potentially observed differences between the biosimilar and the reference product. These studies should use test systems that	See comment on stakeholder 1, lines 140-141.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		are reflective of the underlying disease etiologies. Proposed change: "These studies should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and the product class, using test systems that are reflective of the underlying disease etiologies and current scientific knowledge".	
140-144	14	Comment: We support the notion that there are situations, based on their superior specificity and sensitivity to detect changes, whereby *in vitro* studies may be more sensitive to assessing the potential functional consequences of potentially observed differences between the biosimilar and the reference product than *in vivo* studies. These studies should use test systems that are reflective of the underlying disease etymologies. Proposed change: "Together these assays should broadly cover the spectrum of pharmacological/toxicological aspects known to be of relevance for the reference product and for the product class, using test systems that are reflective of the underlying disease etymologies and current scientific knowledge."	See comment on stakeholder 1, lines 140-141.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
141-144	2	Comment: We appreciate the emphasis on the importance of the in vitro non-clinical studies and the fact that these are considered paramount for the non-clinical comparability exercise. In the current draft guideline the 3Rs principle (replacement, refinement, reduction) is well reflected, and is viewed as an integral part of current efforts to reduce animal testing, since these studies are deemed to be unnecessary based on a scientific background. Even more importantly, superior specificity, sensitivity and reliability of in vitro assays over in vivo animal studies to demonstrate comparability is well justified in the assessment of the functional consequences and clinical relevance of potentially observed differences between the biosimilar and the reference product. The in vitro studies should use test systems that are reflective of the underlying mechanisms of action for the approved indications of the reference product. **Proposed change:** Together, these studies should broadly cover the spectrum of pharmacological/toxicological aspects known to be of clinical relevance for the reference product and the product class, using test systems that are reflective of the underlying mechanisms of action for the approved indications of the reference product and current scientific knowledge.	See comment on stakeholder 1, lines 140-141. The comments on the 3R principles are acknowledged.

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145	4	Comment: Please clarify if these *in vitro* assays need to be validated or would 'scientifically sound' assays suffice.	If validated assays are available, these are considered to represent the preferred option. However, validated assays may not be available for all aspects to be investigated *in vitro*. In such cases, the Applicant should at least justify that the *in vitro* assays used are predictive for the human *in vivo* situation according to current scientific knowledge. See also comment on stakeholder 11, line 145.
145	11	Comment: "*The applicant should justify that the in vitro assays used are predictive for the in vivo situation*". Clarification is needed here – are the results from in vitro assays being compared to the in vivo situation in humans or in animals? And if the latter is the case, then what is the justification for comparing results with animal data which in itself is rarely predictive of the human situation? Proposed change: "*The applicant should justify that the in vitro assays used are predictive for the* ***human*** *in vivo situation*".	Agreed in modified form. The used *in vitro* assays should be predictive for the *in vivo* situation in humans based on the current scientific knowledge. See also comment on stakeholder 4, line 145. *Proposed change – Agreed, in modified form* The Applicant should justify that the *in vitro* assays used are predictive for the human *in vivo* situation, according to current scientific knowledge
145	16	Comment: Why? The purpose of the comparison is to show similarity and not clinical relevance. And in most cases the predictive value of the in vitro assays is unknown. Proposed change:	Not agreed. The purpose of the *in vitro* assays is to show similarity between the reference product and the claimed biosimilar product concerning the whole spectrum of pharmacological/ toxicological aspects known to be of clinical relevance for the reference product and for the product class. *In vitro*

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		delete sentence	comparisons, which lack any relevance for the efficacy and/or safety in humans are usually not expected to contribute to the biosimilar comparability exercise in a meaningful way. It is acknowledged that validated assays may not be available for some pharmaco-toxicological aspects to be evaluated *in vitro* as part of the biosimilar comparability exercise. However, the Applicant should at least show whether/to what extent the used *in vitro* assays can be expected to be predictive for the human *in vivo* situation according to current scientific knowledge. See also comment on stakeholder 4, line 145 and stakeholder 11, line 145.
146-148	6	Comment: It is recommended to add further clarification to the term “stand-alone development”. Proposed change: If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development requiring a full Marketing Authorisation Application, should be considered instead.	Agreed, in modified form. See also comment on stakeholder 17, lines 146-148. *Proposed change – Agreed, in modified form* If the biosimilar comparability exercise indicates that there are significant differences between the biosimilar and the reference medicinal product, making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application, should be considered instead (see ´Guideline on similar biological products`(CHMP/437/04 Rev. 1)). The paragraph was moved to the “Introduction” section of the GL, because the recommendation to consider a stand-alone development may be relevant for all stages of the biosimilar development process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
146-148	8	Comment: In reference to "If the biosimilar comparability exercise indicates early on that there…", we suggest adding a decision tree to better illustrate the comparability exercise. Proposed change: Add to the guideline a graph with a decision tree reflecting actions and decision points of the comparability exercise.	Not agreed. Inclusion of a graph with a decision tree for the biosimilar comparability exercise is not expected to provide additional relevant information for the reader or to improve readability of the GL.
146-148	10	Comment: In reference to "If the biosimilar comparability exercise indicates early on that there…", we suggest adding a decision tree to better illustrate the comparability exercise. Proposed change: Add to the guideline a graph with a decision tree reflecting actions and decision points of the comparability exercise.	See comment on stakeholder 8, lines 146-148.
146-148	13	Comment: Lines 146-148 state "If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-	See comment on stakeholder 8, lines 146-148.

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		alone development, should be considered instead." In order to clarify the meaning of stand-alone development some additional wording is suggested. Proposed change: If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development as would be required for a novel biological medicinal product, should be considered instead."	
146-148	14	**Comment:** In reference to "If the biosimilar comparability exercise indicates early on that there…", we suggest adding a decision tree to better illustrate the comparability exercise. **Proposed change:** Add to the guideline a graph with a decision tree reflecting actions and decision points of the comparability exercise.	See comment on stakeholder 8, lines 146-148.
146-148	16	Self-evident. A company always has this opportunity. This statement does not belong in a guideline. **Proposed change:** delete	Not agreed. As evidenced by the comments received by several stakeholders on this paragraph, there is obviously a need for clarification in the context of this GL.

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146-148	17	Comment: The goal of a biosimilar development is to develop a product which is highly similar to the reference product. Therefore where necessary, (non-)clinical data should be used only to confirm this high similarity; these (non-)clinical data should not be used to justify 'significant' differences (like e.g. major changes in the glycosylation pattern). Lines 146-148 could be read as to suggest that significant differences in quality attributes still can be overruled by subsequent (non-)clinical studies. Proposed change: If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product contradicting biosimilarity~~making it unlikely that biosimilarity will eventually be established~~, a stand alone development should be considered instead.	See comment on stakeholder 6, lines 146-148.
149	16	The problem of this part of the revision is the lack of distinction between the use of animals for similarity issues or to show the significance of product characteristics of the biosimilar. For similarity there may be arguments for PK/PD comparisons in relevant species. For e.g. a not very well known formulation local tolerance studies may be relevant, not	Not agreed. *In vivo* animal studies, if considered necessary (see step 2 of the step-wise approach) are part of the overall biosimilar comparability exercise and serve similarity issues whether performed in a comparative or a non-comparative way. Therefore, rewriting of section 4.2 with the proposed distinction is not considered necessary.

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		necessarily in a comparative way with the reference. Proposed change: rewrite the paragraph with this distinction	
149-153	7	Comment: Propose to include that in-vivo studies may be needed, unless there is significant body of manufacturing experience and an associated body of clinical data.	Not agreed. (i) As detailed in section 4.2 of the GL, the need for additional *in vivo* animal studies is determined in essence on basis of the results of the quality and of the non-clinical *in vitro* part of the biosimilar comparability exercise. (ii) Taking into account the legal basis of the biosimilar approach in the EU, usually at least 10 years of clinical experience with the reference product will be available.
149-175	20	Comment: ("Step 2: Determination of the need for in vivo studies"): The Draft Guideline states that non-clinical *in vivo* studies "may be necessary" to complement the results obtained through *in vitro* studies. It also suggests, "If the comparability exercise in the *in vitro* studies in step 1 is considered satisfactory and no factors of concern are identified in step 2, or these factors do not block direct entrance into humans, an *in vivo* animal study may not be considered necessary." We remain firmly of the view that the CHMP should not permit testing of any biological product in humans without at least some testing in another species. The nature and extent of this testing should be determined	Not agreed. See also comment on stakeholder 8, lines 129-133. (i) The non-clinical biosimilar comparability exercise is based on a comprehensive analytical comparison of the physicochemical and biological properties of the claimed biosimilar and the chosen reference product, complemented by a comprehensive comparison of the spectrum of oharmaco-toxicological effects known to be of relevance for the reference product and the product class in appropriate *in vitro* assays (step 1 of the non-clinical evaluation). If these data are considered satisfactory and no issues are identified which would block direct entrance into humans, *in vivo* animal studies are not expected to reveal additional unknown or enhanced activities mediated by targets which

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		on a case-by-case basis. In the early stages of a biosimilar development programme, an applicant may have insufficient experience with or information about the proposed product to identify and assess uncertainties about the proposed biosimilar's safety. We believe that the final guideline should state that some testing in a representative non-human species generally will be expected unless the applicant can demonstrate that there is no anticipated safety risk that might be detected in animals. Permitting the clinical testing or marketing of a biological product that has never been subject to *in vivo* testing could pose safety risks. Animal testing may detect differences between the products that were not detected through analytical testing, such as differences with respect to inactive ingredients, contaminants, and the presence of aggregates. Individuals enrolled as study subjects in clinical studies also hold the reasonable expectation that the proposed biosimilar product, like the vast majority of pharmaceuticals, has been tested in non-human animals. In light of these patient expectations and the principles of informed consent, the final guideline should require sponsors who forgo *in vivo* testing to (1) inform initial human study subjects that no prior animal testing has been conducted in order to explain relevant risks; and (2) obtain consent from the study subjects.	have not been previously described to be clinically relevant for the reference product (i.e. off-target pharmacology/toxicology). Taking into account the 3R principles and the fact that there are usually at least 10 years of clinical experience with the reference product, additional *in vivo* animal studies should only be considered in specific cases where remaining uncertainties in step 1 and 2 of the non-clinical evaluation justify the conduct of such experiments. (ii) Recommendations for clinical study authorisation are not within the scope of this GL.

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149-211	17	Comment: The current draft text on *in vivo* studies including the discussion on the need for *in vivo* studies is too much suggestive of the idea that significant differences in quality attributes may be overruled by *in vivo* studies. Especially the bullet points "*Presence of relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).*" and "*Significant quantitative differences in quality attributes between the intended biosimilar and the reference product*." suggest that these significant differences could be overruled. This is not in line with the view that biosimilar and reference product should be highly similar. Also the terminology 'level of concern' is suggestive of the possibility that differences between biosimilar and reference product that raise concern still could be acceptable as long as these concerns are not confirmed in an animal study. This is the wrong message. Furthermore the limited design of animal studies leads to a very low sensitivity to detect relevant differences. Therefore animal studies would only be anticipated in exceptional cases. This should be expressed much more clearly. Proposed change: 4.2. ~~Step 2: Determination of the need for~~ *In vivo*	Not agreed/Partly agreed. It is not agreed that the wording of the GL is too much suggestive of the idea that significant differences in quality attributes may be overruled by *in vivo* animal studies. For clarification, a respective paragraph is part of the GL (this paragraph has been moved to the "Introduction" section of the GL, see comment on stakeholder 6, lines 146-148). If the biosimilar comparability exercise indicates that there are significant differences between the biosimilar and the reference medicinal product, making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application, should be considered instead (see ´Guideline on similar biological products`(CHMP/437/04 Rev. 1)). *Proposed change – Not agreed.*

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		studies It is acknowledged that biotechnology-derived proteins may mediate *in vivo* effects that cannot be fully elucidated by *in vitro* studies. Generally, these aspects can be assessed clinically. However, in exceptional cases ~~Therefore,~~ non-clinical evaluation in *in vivo* studies may be necessary to provide complementary information, provided that a relevant *in vivo* model with regard to species ~~or~~ and design is available. ~~Factors to be considered when the need for *in vivo* non-clinical studies is evaluated, include, but are not restricted to:~~ ~~• Presence of relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).~~ ~~• Significant quantitative differences in quality attributes between the intended biosimilar and the reference product.~~ ~~•~~ An example of such an exceptional case could be the introduction of relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins. ~~Although each of the factors mentioned above do not necessarily warrant *in vivo* testing, these issues should be considered together to assess the level of concern~~	

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		~~and whether there is a need for *in vivo* testing.~~ If the comparability exercise <u>for the physicochemical and biolological characteristics and the</u> ~~in~~ the non-clinical *in vitro* studies ~~in step 1~~ is considered satisfactory and no <u>issues</u> ~~factors of concern~~ are identified ~~in step 2, or these factors do not~~ <u>which would</u> block direct entrance into humans, an *in vivo* animal study may not be considered necessary. If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot sufficiently be characterised on a quality and *in vitro* level, *in vivo* studies may be necessary. Applicants should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers. If there is a need for additional *in vivo* information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered. If a relevant *in vivo* animal model is not available the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk. ~~4.3. Step 3: *In vivo* studies~~ If an *in vivo* evaluation is deemed necessary,……	*Proposed change – Agreed, in modified form* … If the biosimilar comparability exercise for the physicochemical and biological characeristics and the non-clinical *in vitro* studies (step 1) are considered satisfactory and no issues are identified in step 2 which would block direct entrance into humans, an *in vivo* animal study is not usually considered necessary. …

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152-153 and 172-173	13	Comment: there is a redundancy between lines 152-153 and 172-173. Even if there is a need for additional in vivo information, if there is no availability of a relevant animal species or model, then in vivo studies would not be able to provide appropriate information to aid with the comparability guideline. We propose to delete lines 172-173 and add to lines 152-153 the examples of relevant models as specified on line 173.	Not agreed. While in lines 152-153 of the current GL text the principle request for a relevant animal model is expressed, examples of such models are provided in lines 172-173. The proposal for text revision provided in the comment is not expected to significantly improve the GL wording with regard to understandability and/or readability.
154-161	8	Comment: It should be recognised that new impurities may be present in a biosimilar that are not picked up by the developed analytical tests. In addition, another factor to be considered in evaluating the necessity and scope of *in vivo* studies is the inability to rule out differences in relevant quality attributes due to the difficulty in characterizing a given product. This difficulty could be due to the inherent complexity or heterogeneity of a product or due the limited clinical or regulatory experience with a given product or class. This technical challenge is alluded to ca. line 168, but line 168 only refers directly to challenges inherent to the biologic and does not directly address challenges inherent to characterizing a given product or class. While the draft Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1) suggests that the biosimilar concept is more difficult to apply for	Not agreed. It is not agreed that any specific safety or toxicity concern that has previously been identified for the reference product should present a potential trigger for *in vivo* animal studies. As outlined in the comment on stakeholder 8, lines 129-133 and stakeholder 20, lines 149-175, an evaluation of potential toxicological effects of the claimed biosimilar in *in vivo* animal studies should only be considered in specific cases where remaining uncertainties in step 1 and 2 of the nonclinical evaluation specifically justify the conduct of such studies. The following wording is <u>not agreed</u> as a trigger for additional in vivo animal studies The inability to rule out relevant quality differences between the reference product and the biosimilar candidate due to difficulties in characterizing the product, such as for highly complex products or biological substances arising from extraction from biological sources

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		difficult-to-characterize biologics, it does not rule this possibility out. We suggest that it is especially critical that potential safety issues with such products should be evaluated in a step-wise fashion, starting with in vivo non-clinical studies. Finally, we also suggest that it is important to consider any safety concerns that have been identified for the reference product which may be confirmed by in vivo testing. Proposed change: Consider adding the following text: 'Factors to be considered when the need for in vivo non-clinical studies is evaluated, include, but are not restricted to: • Presence of relevant quality attributes that have not been detected in the reference product (e.g. now post-translational modification structures). • Significant quantitative differences in quality attributes between the intended biosimilar and the reference product • Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology derived proteins.	and/or those for which little clinical and regulatory experience has been gained. a) The present GL deals with biosimilar medicinal products containing biotechnology-derived proteins as active substance. Therefore, the reference to biological substances arising from extraction from biological substances is not relevant for this GL. b) According to the state of art, the analytical tools available for characterization of biotechnology-derived proteins are expected to usually allow for a sufficiently detailed characterization to detect significant quality differences between the reference product and the claimed biosimilar product. c) Taking into account the underlying legislation in the EU, usually at least 10 years of clinical experience are expected to be available for the reference product.

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		• Any specific safety or toxicity concerns that have previously been identified for the reference product. The inability to rule out relevant quality differences between the reference product and the biosimilar candidate due to difficulties in characterizing the product, such as for highly complex products or biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained.'	
154-161	14	Comment: An additional factor to be considered in evaluating the necessity and scope of *in vivo* studies is the inability to rule out differences in relevant quality attributes due to the difficulty in characterizing a given product. This difficulty could be due to the inherent complexity or heterogeneity of a product or due to the limited clinical or regulatory experience with a given product or class. This technical challenge is alluded to in line 168, but line 168 only refers directly to challenges inherent to the biologic and does not directly address challenges inherent to characterizing a given product or class. While the draft Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1) suggests that the biosimilar concept is more difficult to apply for difficult-to-characterize biologics, it does not rule this	See comment on stakeholder 8, lines 154-161.

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		possibility out. We suggest that it is especially critical that potential safety issues with such products should be evaluated in a step-wise fashion, starting with in vivo non-clinical studies. Proposed change: Consider adding the following text: 'Factors to be considered when the need for in vivo non-clinical studies is evaluated, include, but are not restricted to: • Presence of …. • Significant quantitative differences in quality … • Relevant differences in formulation….. The inability to rule out relevant quality differences between the reference product and the biosimilar candidate due to difficulties in characterizing the product.	
154-161	15	Comment: We propose to add the sentences in red as follows Proposed change: Factors to be considered when the need for in vivo non-clinical studies is evaluated, include, but are not restricted to: • Presence of relevant quality attributes that have	Not agreed. *Proposed changes – Not agreed* (i) *In vitro* characterization is not sufficient due to the complexity of the molecule. Not agreed: see comment on stakeholder 8, lines 154-161. (ii) An impact on immunogenicity cannot be excluded with reasonable certainty.

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		not been detected in the reference product (e.g. new post-translational modification structures). • Significant quantitative differences in quality attributes between the intended biosimilar and the reference product. • In vitro characterisation is not sufficient due to the complexity of the molecule and an impact on immunogenicity cannot be excluded with reasonable certainty Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins.	Not agreed: Immunogenicity for patients has to be characterized in the clinical setting. Results of the evaluation of immunogenicity of biotechnology-derived proteins in *in vivo* animal studies are usually not predictive for the human *in vivo* situation.
156-157	19	Comment: "Presence of relevant quality attributes that have not been detected in the reference product" is unclear as an example of a factor to be considered when the need for in vivo non-clinical studies is evaluated (as there may be also cases when relevant quality attributes that have been detected in the reference product were not found for the intended biosimilar product). The lines 156-157 are therefore recommended to be deleted as the aspect of differences in quality attributes is sufficiently discussed in lines 158-159.	Not agreed. It is not agreed to delete lines 156-157. In lines 156-157, reference is made to qualitative differences in quality attributes, while in lines 158-159 reference is made to quantitative difference s in quality attributes. Both aspects should be mentioned in the GL.
160-161	5	Comment: Regarding in vivo study requirement, it would be	Not agreed. It is agreed and already mentioned in the current GL wording

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		better to limit the situation to using novel excipient in formulation. In some cases where the original formulation composition has existing patent, applicants may use other composition of excipients widely used for biotechnology-derived proteins to avoid infringement of patent. In this case, it is thought to be sufficient to conduct only in vitro assay for comparability, provided that the comparability data obtained from in vitro studies are considered satisfactory and that novel excipients were not used for the modified formulation. This is also consistent with 3Rs principle (replacement, refinement, reduction). Proposed change: It is recommended to change the guideline to consider the in vivo nonclinical studies in relation to the differences in formulation when "only the novel excipients are used".	that differences in formulation could trigger the conduct of *in vivo* animal studies. However, as outlined in section 4.2 of the GL, *in vivo* animal studies may also be considered in specific other cases.
160-162	1	Comment: BIO believes that specific safety or toxicity concerns identified for the reference product should be considered when the need for *in vivo* non-clinical studies is evaluated. An additional factor to be considered in evaluating the necessity and scope of *in vivo* studies is the inability to rule out differences in relevant quality attributes due to the difficulty in	See comment on stakeholder 8, lines 154-161.

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		characterizing a given product. This difficulty could be due to the inherent complexity or heterogeneity of a product or due to the limited clinical or regulatory experience with a given product or class. BIO suggests that it is especially critical that potential safety issues with such products be evaluated in a step-wise fashion, starting with *in vivo* non-clinical studies. Proposed change: "• Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins. • Any specific safety or toxicity concerns that have previously been identified for the reference product. • The inability to rule out relevant quality differences between the reference product and the biosimilar candidate due to difficulties in characterizing the product, such as for highly complex products, biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained."	
165-167	4	Comment: Immunogenicity: The GL states that the length of the follow up is normally one year for products with chronic administration but can be shorter if justified. The justifications should take into account the characteristics of the product and the experience	(i) Clinical trial authorisation during development of a biosimilar is within the realm of the national regulatory

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Who will decide and how will the decision be made regarding if the results from the comparability exercise in *in vitro* studies are satisfactory? Comment: It is important to note that toxicological assessments would not necessarily be predictable through *in vitro* assays	authorities. For marketing authorisation of a biotechnology-derived biosimilar, EMA will be responsible for assessment. (ii) See comment on stakeholder 20, lines 149-175.
165-167	11	Comment: Based on scientific consensus from review papers, these studies are rarely needed and the language should be adjusted to this effect. Proposed change: If the comparability exercise in the in vitro studies in step 1 is considered satisfactory and no factors of concern are identified in step 2, or these factors do not block direct entrance into humans, an in vivo animal study is not usually ~~may not be~~ considered necessary"	Agreed, in modified form. See also comment on stakeholder 17, lines 149-211. *Proposed change – Agreed, in modified form* If the biosimilar comparability exercise for the physico-chemical and biological characteristics and the non-clinical *in vitro* studies (see step 1) are considered satisfactory and no issues are identified in step 2 which would bock direct entrance into humans, an *in vivo* animal study is not usually considered necessary.
165-167	15	Comment: We suggest to add the sentences in red as follows Proposed change: "If the comparability exercise in the *in vitro* studies in step 1 is considered satisfactory and no factors of concern are identified in step 2, or these factors do not block direct entrance into humans, an *in vivo* animal	Not agreed. Immunogenicity for patients has to be characterized in the clinical setting. Results of the evaluation of immunogenicity of biotechnology-derived proteins in *in vivo* animal studies are usually not predictive for the human *in vivo* situation.

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		study may not be considered necessary. However prior to decide entrance into human, it should be evaluated the need of performing preclinical immunogenicity tests in animals or in cell lines.	
168-171	11	Comment: "*If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot sufficiently be characterised on a quality and in vitro level, in vivo studies may be necessary. Applicants should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers*". It is a legal requirement in the EU (Directive 2010/63/EC) that animal tests are not conducted if an alternative approach is scientifically possible. An alternative approach can be to use an ethically conducted human study. The language towards an either/or in this case should therefore be adjusted. PK/PD studies of biologics in animals are often not reliable because of species differences which include host immune response to the substance and differences in target-binding properties. "*It is well established that the targeted-mediated clearance and antidrug-antibody-mediated clearance for therapeutic biologics are species dependent […] Thus, common laboratory animals may not always be relevant for*	Comments are acknowledged.

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		prediction of ADME profiles of therapeutic biologics in humans". (Xu and Vugmeyster, 2012). In addition to tests in volunteers, theoretical analyses of ADME profiles could also be conducted using computer programs that can predict the biophysical and biochemical properties of biologics, such as size, affinity and target antigen. (Xu and Vugmeyster, 2012). Proposed change: "*If product-inherent factors that impact PK and/or biodistribution, like extensive glycosylation, cannot sufficiently be characterised on a quality and in vitro level, in vivo studies may be necessary. Applicants should then carefully consider if these should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers*". According to Directive 2010/63/EC unnecessary animal studies are unethical and should be avoided. If healthy volunteer studies are possible then animal studies should not be conducted. Evidence that the animal model is relevant for PK/PD data should be provided. Use of computer models should also be considered.	*Proposed change – Not agreed.* Reference to directive 2010/63/EC and the 3R principles is already contained in section 4.3 of the GL and does not need to be repeated here (see also comment on stakeholder 1, lines 179-180).
168-175	2	Comment: The draft guideline states that in vivo studies may be necessary, if product-inherent factors such as extensive glycosylation as well as new formulation	Comments are acknowledged.

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		excipients that impact PK, PD and/or biodistribution, cannot sufficiently be characterised on a quality and in vitro level. The applicant then should carefully investigate whether these studies should be performed in animals or in healthy volunteers. Further, if a relevant in vivo model is not available, the applicant may choose to proceed to human studies taking into account principles and applicable measures to mitigate any potential risk. EBG fully supports this science-based stepwise approach. However, EBG's member companies have experienced that local ethic committees (ECs) are not yet fully informed about the EU regulators' thinking on the biosimilar non-clinical and clinical development, since they have received the request to conduct additional animal testing prior to initiating human studies. Therefore we would like to suggest that such a recommendation may be (1) included into the Scientific Advice documents so that it can be shown to National Competent Authorities and ECs; and (2) distributed and made known within the entire EU regulatory world among all member states.	Mentioned issues are not within the scope of this GL.
168-175	10	Comment:	See comments on stakeholder 2, lines 168-175.

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		The draft guideline states that *in vivo* studies may be necessary, if product-inherent factors such as extensive glycosylation as well as new formulation excipients that impact PK, PD and/or biodistribution, cannot sufficiently be characterised on a quality and *in vitro* level. The applicant then should carefully investigate whether and what kind of animal studies should be performed. Further, if a relevant *in vivo* model is not available, the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk. Novartis fully supports this science-based stepwise approach. However, we have made the experience that local ethic committees are not yet fully informed about the EU regulators' current thinking about biosimilars. We have received the request for additional animal testing prior to proceeding into humans. Therefore we would like to suggest that such a recommendation is (3) Included into the Scientific Advice document so that it can be shown to local HAs and ECs, and (4) Also distributed and made known within the entire EU regulatory world among all member states.	
168-175	14	Comment:	See comments on stakeholder 2, lines 168-175.

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		We support the science-based stepwise approach outlined in Section 4.2. However, in practice some member companies have experienced that local ethic committees are not yet fully informed about the EU regulators' current thinking about biosimilars and have requested additional animal testing prior to proceeding into humans, which delays a positive opinion for the start of a clinical study. It would facilitate communication if a product specific recommendation is explicitly included into the Scientific Advice document so that it can be shown to local HAs and ECs. Proposed change:	
172-173	15	Comment: We suggest to add the sentences in red as follows Proposed change: Some classes of therapeutic biologics may have very limited interspecies crossreactivity or pronounced immunogenicity, or may work by mechanisms that are not known to be conserved between animals and humans; in these cases, safety data from animal studies may be very limited in scope and interpretability. If there is a need for additional in vivo information, the	Not agreed. It is agreed that some classes of therapeutic biologics may have very limited interspecies crossreactivity or pronounced immunogenicity or may work by mechanisms that are not known to be conserved between animals and humans; in these cases, safety data from animals may be very limited in scope and interpretability. However, these well known facts are true not only for biosimilars but also for the reference products and biotechnology-derived proteins in general and therefore, do not need to be specifically mentioned in this biosimilar GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered.	
172-175	11	Comment: "*If there is a need for additional in vivo information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered. If a relevant in vivo animal model is not available the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk*". What is defined as a "relevant animal species" or "relevant animal model"? How is this determined? "*In the absence of scientific justification, the repetition of animal and clinical studies could be considered unethical (apart from being prohibitively expensive)*." (McCamish and Woollett, 2012). Proposed change: "*If there is a need for additional in vivo information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered. If a relevant in vivo animal model is not available the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk*".	See also comment on stakeholder 11, lines 168-171. (i) A relevant species is defined as a species in which the active substance is pharmacologically or toxicologically active (see ICH S6 GL). *(ii) Proposed change – Not agreed.* Reference to Directive 2010/63/EC and the need to take into account the 3R principles are already mentioned elsewhere in the GL (see also comment on stakeholder 1, lines 179-180). Therefore, the proposed additional paragraph is not considered to provide relevant additional information for the reader.

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		Both the need for an in vivo animal study and the absence of a need for an in vivo animal study should be adequately justified, taking into account the analytical data and other in vitro studies. According to Directive 2010/63/EC unnecessary animal studies are unethical and should be avoided.	
174-175	4	Comment: Would a discussion with the Agency be required to determine the path or can the applicant proceed with the development if appropriate justifications are included in the marketing authorisation dossier?	It is within the responsibility of the biosimilar developer to provide an adequate dossier for marketing authorisation application. However, biosimilar developers are encouraged to contact the EMA and ask for scientific advice during product development.
176	7	Comment: take into account the therapeutic index or safety hazard of the drug class	See comment on stakeholder 8, lines 129-133 and stakeholder 20, lines 149-175.
176	16	This section of the revision is very generic and applicable to animal studies in general. Most of it can be deleted. Proposed change: Merge this section with the previous one and delete most of the discussion that is not specific for biosimilars.	Not agreed. As evidenced by the comments received on GL section 4.3, the guidance provided is considered important and, with regard to readability, preferred to be maintained as a separate chapter.
177-178	8	Comment: The precautionary principle should be applied for *in vivo* studies. To reflect this, the word “necessary” in line 177 should be exchanged with “relevant”. Proposed change:	Not agreed. As detailed in the comments on stakeholder 8, lines 129-133, and stakeholder 20, lines 149-175, and in line with Directive 2010/63/EC, non-clinical *in vivo* studies should only be considered in specific cases, i.e. when considered necessary to resolve issues not sufficiently covered by the physico-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Consider amending the text as follows: 'If an *in vivo* evaluation is deemed ~~necessary~~ relevant, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information.'	chemical and biological analytical characterization and by step 1 of the non-clinical evaluation (see chapter 4.2 of the GL).
177-178	14	Comment: The precautionary principle should be applied for *in vivo* studies. To reflect this, the word "necessary" in line 177 should be exchanged with "relevant". Proposed change: If an *in vivo* evaluation is deemed ~~necessary~~ relevant, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information.	See comment on stakeholder 8, lines 177-178.
177-211	9	Comment: We note that the WHO 2009 guideline, the 2012 Indian guideline and others internationally, all strongly influenced by the past CHMP/EMA position which has changed since about 2012, impose a higher nonclinical burden. They are not aligned with the new EMA position. Between 2006-2011 EU approvals required more animal tox, tolerance and safety studies. Perhaps this evolving EMA position and change needs to be mentioned for clarity due to the strong international influence of the EMA biosimilar experience.	Comments are acknowledged. The main changes to be introduced in the revised GL version have been described in the respective concept paper and are now listed in the "Introduction" section of this GL.
179-180	1	Comment: BIO suggests providing a reference to the 3R's	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		principle to avoid any risk of ambiguity. Proposed change: "The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any in vivo study."	*Proposed change – Agreed.* The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any *in vivo* study.
179-180	8	Comment: Referring to "The principles of the 3R's (replacement, refinement, reduction) should be considered when designing any in vivo study." we suggest to provide a reference to the 3R's principle to avoid any risk of ambiguity. The direct inclusion in the current wording of 3 R's vis-à-vis the absence of a mention of the principle of safeguarding humans in clinical trials gives an imbalance that could be interpreted as 3R's being prioritised above safeguarding clinical trial subjects. It is therefore suggested to make it clear that the 3R's are not the only consideration. Proposed change: Consider amending the text as follows: 'The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should also be considered when designing any *in vivo* study.'	See comment on stakeholder 1, lines 179-180.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
179-180	10	Comment: Referring to "The principles of the 3R's (replacement, refinement, reduction) should be considered when designing any in vivo study.", we suggest to provide a reference to the 3R's principle to avoid any risk of ambiguity. Proposed change: "The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any in vivo study."	See comment on stakeholder 1, lines 179-180.
179-180	14	Comment: Referring to "The principles of the 3R's (replacement, refinement, reduction) should be considered when designing any in vivo study.", we suggest to provide a reference to the 3R's principle to avoid any risk of ambiguity. Furthermore, while fully acknowledging and supporting the importance of the principles of 3R we believe that the guideline should avoid any suggestion that these are put above safeguarding clinical trial subjects Proposed change: "The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should also be considered when designing	Agreed, with modification. See comment on stakeholder 1, lines 179-180. *Proposed change – Agreed, in modified form.* The principles of the 3Rs (replacement, refinement, reduction) according to Article 4 of Directive 2010/63/EU should be considered when designing any *in vivo* study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		any in vivo study."	
184-186	19	Comment: The need of conducting non-clinical in vivo PK/PD studies assessing concentration-response relationship in the therapeutic dose range in humans may be questionable from the 3Rs principle perspective. Non-clinical PK/PD in vivo studies may not always be necessary to evaluate concentration-response relationship, in particular when this correlation was clearly shown in the in vitro studies, especially if these in vitro studies were conducted with the use of human receptor/cell lines. Moreover, the non-clinical in vivo PK/PD studies may not necessarily be representative for the clinical outcome. Proposed changes: The following sentence is proposed to be added in line 186: <u>In vivo concentration-response assessment may be waived whenever such correlation was clearly shown in the in vitro studies or if appropriately justified.</u>	Partly agreed. Whether PD and/or PK of reference and claimed biosimilar product should be compared in non-clinical *in vivo* studies by performing a concentration-response assessment covering the therapeutic range in humans relies on a case-by-case decision based on the totality of available data. A general waiver for an *in vivo* concentration-response assessment, if such a relation was clearly shown *in vitro*, is therefore not supported (additional ADME factors may influence the concentration-response *in vivo*). *Proposed change – Partly agreed.* When the model allows, the PK and PD of the biosimilar and the reference product should be quantitatively compared, if not otherwise justified by including a concentration-response assessment covering the therapeutic dose-range in humans.
188-189	11	Comment: "*The conduct of standard repeated dose toxicity studies in non-human primates is not usually recommended*". The reasons for this statement should be clarified. Why	Comments are acknowledged. *Proposed change* In accordance with the 3R principles, for safety studies a flexible approach should be considered, in particular if non-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		aren't they usually recommended? Is it due animal welfare concerns? Are the tests not considered predictive enough?	human primates are the only relevant species. The conduct of standard repeated dose toxicity studies in non-human primates is usually not recommended.
189	8	Comment: If only one dose is selected for the repeat dose toxicity study it should be justified on basis of expected toxicity in light of experience with the reference product. Generally a dose to the high end of the dose range of the reference product would be recommended, bearing in mind that if the dose tested is too high it may induce marked toxicological effects for both the reference product and the biosimilar, masking any possible difference that may be apparent at lower doses. Proposed change: Consider amending the text as follows: 'If appropriately justified, a repeated dose toxicity study with refined design (e.g~~. using just one dose level of biosimilar and reference product and/or~~ just one gender and/or no recovery animals) or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions) may be considered. For repeated dose toxicity study where only one dose is selected this would usually be selected at the high end of the dosing range and should be justified on the basis of expected toxicity of the reference product.	Comments are acknowledged. *Proposed change – Agreed, in modified form* If appropriately justified, a repeated dose toxicity study with refined design (e.g. using just one dose level of biosimilar and reference product and/or just one gender and/or no recovery animals) or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions) may be considered. For repeated dose toxicity studies where only one dose is selected, this would usually be selected at the high end of the dosing range and should be justified on the basis of expected toxicity of the reference product

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
189-192	4	Comment: Could the Agency provide clarification in regards to the requirements of recovery cohorts as these are not needed in all *in vivo* studies.	Whether recovery cohorts are required should be decided on a case-by-case basis, taking into account the totality of available data
189-192	19	Comment: It is fully acknowledged that standard repeated-dose toxicity studies in non-human primates are not recommended. However, once these studies are judged to be needed, they should allow gaining as much information as possible, as stated in lines 178-179 of the present Guideline. In this context, in-life observational animal studies, which are suggested as one of the alternatives to standard repeated-dose toxicity studies, are not likely to provide any valuable information on discrete differences between the biosimilar and the reference product. Parameters proposed to be investigated, i.e. clinical signs, body weight and vital functions, in the vast majority of cases will not be sensitive enough to detect minute differences between reference and biosimilar product properties. Therefore, such alternative to standard toxicological studies in non-human primates should not be proposed in the Guideline. Proposed changes: If appropriately justified, a repeated dose toxicity study with refined design, ~~(~~e.g. using just one dose	Not agreed. It is not agreed that in-life observation studies are not likely to provide any valuable information on discrete differences between the biosimilar and the reference product. Factors such as e.g. body weight or food consumption may in fact be sensitive ´early` indicators of toxicity. *Proposed change – Not agreed.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level of biosimilar and reference product and/or just one gender and/or no recovery animals~~) or an in-life evaluation of safety parameters (such as clinical signs, body weight and vital functions)~~ may be considered.	
190	14	Comment: If one dose is selected for the repeat dose toxicity study that should be justified on basis of expected toxicity in light of experience with the reference product. Generally a dose to the high end of the dose range of the reference product would be recommended. Proposed change: "If appropriately justified, ……..with refined design (e.g. using just one dose level of biosimilar and reference product, generally to the high end of the dose range of the reference product, and/or just one gender….")	See comment on stakeholder 8, line 189.
193-194	4	Comment: The assessment of impact of impurities can be included with the repeated dose studies.	Comments are acknowledged. See also comment on stakeholder 13, lines 193-197.
193-194	11	Comment: "*The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended*".	A relevant species is defined as a species in which the active substance is pharmacologically or toxicologically active (see ICH S6 GL). See also comment on stakeholder 11, lines 172-175.

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		Again, how is relevance/non-relevance demonstrated? According to Directive 2010/63/EC unnecessary animal studies are unethical and should be avoided.	
193-197	13	Comment: The draft guideline revision states that “The conduct of toxicity studies in non-relevant species (i.e. to assess unspecific toxicity only, based on impurities) is not recommended.”, and later states that in such cases “The level of such impurities should be kept to a minimum, which is the best strategy to minimise any associated risk.” Can the EMA clarify if this approach includes impurities with unknown toxicological properties? In such circumstances, would the EMA consider that the worst case scenario of using a Threshold of Toxicological Concern based on the impurity being a potent genotoxic carcinogen (as per CPMP/SWP/5199/02 EMEA/CHMP/QWP/251344/2006) should be used in the risk assessment, unless this could be justified otherwise?	Biotechnology-derived proteins are not within the scope of the genotoxicity GL cited by stakeholder 13. In accordance with the ICH S6 GL, the present GL recommends to keep the level of impurities to a minimum as best strategy to minimize any associated risk. As also mentioned in the GL, the conduct of *in vivo* animal toxicity studies, just for the purpose to study ´unspecific toxicity` by (process-related) impurities, is not recommended.
196	7	Comment: Proposed change: Impurities should be representative of the clinical grade material	Agreed. The revised GL contains the recommendation to use for the non-clinical evaluation batches of the biosimilar product representative of that intended for clinical use (see GL section 4.1)
200-201	1	Comment: Differences with the potential to impact	

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		immunogenicity may not be predictive when extrapolating data from animals to humans, and such effects are likely to be very rare and difficult to ascertain. Usually assessment in clinical studies is most relevant and preferred. Since the word “quality” is often used as a general description of excellence of standard or level, this may lead to misunderstandings. BIO, therefore, suggests deleting, since the types of differences referred to in this sentence are already described in the sentence before. Proposed change: “These ~~quality~~ differences may have an effect on immunogenic potential and the potential to cause hypersensitivity.”	
200-201	8	Comment: Differences with the potential to impact immunogenicity may not be predictive when extrapolating data from animals to humans, and such effects are likely to be very rare and difficult to ascertain. Usually assessment in clinical studies is most relevant and preferred. Since the word “quality” is often used as a general description of excellence of standard or level, this may lead to misunderstandings. We therefore suggest to delete this word, since the type of differences referred	Comments are acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to in this sentence are already described in the sentence before. Proposed change: Consider amending the text as follows: 'These ~~quality~~ physico-chemical differences may have an effect on immunogenic potential and the potential to cause hypersensitivity.'	*Proposed change – Agreed.* These differences may have an effect on immunogenic potential and the potential to cause hypersensitivity.
200-201	10	Comment: Differences with the potential to impact immunogenicity may not be predictive when extrapolating data from animals to humans, and such effects are likely to be very rare and difficult to ascertain. Usually assessment in clinical studies is most relevant and preferred. Since the word "quality" is often used as a general description of excellence of standard or level, this may lead to misunderstandings. We therefore suggest to delete this word, since the type of differences referred to in this sentence are already described in the sentence before. Proposed change: "These ~~quality~~ differences may have an effect on immunogenic potential and the potential to cause hypersensitivity."	See comments on stakeholder 8, lines 200-201.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
200-201	14	Comment: Since the word “quality” is often used as a general description of excellence of standard or level, this may lead to misunderstandings. We therefore suggest to delete this word, since the type of differences referred to in this sentence are already described in the sentence before. Proposed change: “These ~~quality~~ differences may have an effect on immunogenic potential and the potential to cause hypersensitivity.”	See comments on stakeholder 8, lines 200-201.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
201-202	11	Comment: "*It is acknowledged that these effects are difficult to predict from animal studies and should be further assessed in clinical studies*". There is a substantial amount of evidence to prove that immunogenicity studies animals offer no predictive value in humans. Therefore, this statement should be much stronger. One of the biggest areas of concern is the potential immunogenic capabilities of biosimilars in patients. The mechanisms of how these products elicit immunological responses in patients are poorly understood and cannot be adequately predicted from animal tests; "*At present, only clinical trials can provide definitive data, and these data may only appear after the later stages of drug development or even after drug approval*". (Berkowitz et al., 2013). Proposed change: It is acknowledged that these effects are impossible ~~difficult to~~ predict from animal studies and should be ~~further~~ assessed in clinical studies rather than in animals.	Not agreed. As expressed in the current GL wording, it is recommended to assess immunogenicity in clinical studies. Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of *in vivo* (PK/TK) studies in animals. However, since this is a rapidly evolving field, the wording proposed by stakeholder 11, that it is impossible to predict immunogenicity in humans from animal studies in considered too strong. *Proposed change - Not agreed*.
203-205	8	Comment: The scientific basis of taking blood samples is not	Comments are acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		completely clear in this context. Additional explanation is needed. Proposed change: Please add an explanation for the requirement of taking blood samples.	*Proposed change* Therefore, blood samples should be taken and stored for future evaluations of pharmacokinetic/toxicokinetic data if then needed.
203-205	10	Comment: The scientific basis of taking blood samples is not completely clear in this context. Additional explanation is needed.	See comment on stakeholder 8, lines 203-205.
203-205	14	Comment: The scientific basis of taking blood samples is not completely clear in this context. Additional explanation is needed. Proposed change: Please add an explanation for the requirement of taking blood samples	See comment on stakeholder 8, lines 203-205.
203-205	15	Comment: We suggest to add the sentences in red as follows Proposed change: Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of in vivo studies in	See comment on stakeholder 11, lines 201-202. *Proposed change – Not agreed.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		animals. In particular, the relevance of the animal models used in non-clinical testing should be understood, particularly with regards to the activity of the biosimilar formulation. Therefore, blood samples should be taken and stored for future evaluations if then needed.	
206-207	19	Comment: In the current version of the guideline, mutagenicity studies are recommended to be listed (together with safety pharmacology, reproduction toxicology and carcinogenicity studies) as not required for non-clinical testing of biosimilars. Proposed changes: Studies regarding safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity are not required for non-clinical testing of biosimilars.	Not agreed. According to the ICH S6 GL, mutagenicity studies are usually not required for biotechnology-derived proteins. Taking into account this general recommendation, absence of mutagenicity studies does not need to be specifically mentioned in this GL.
209	1	Comment: BIO recommends revising for clarity. Proposed change: "...with the intended clinical route of administration, local tolerance..."	Agreed. *Proposed change - Agreed* Studies on local tolerance are usually not required. However, if excipients are introduced for which there is no or little experience with the intended clinical route of administration, local tolerance may need to be evaluated.
209	8	Comment: Suggesting adding the following text for clarity.	See comment on stakeholder 1, line 201.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending the text as follows: "…with the intended clinical route of administration"	
209	14	Proposed change: "…with the intended clinical route of administration"	See comment on stakeholder 1, line 201.
213-217	16	Comment: Not a specific issue for biosimilars Proposed change: delete	True. Nevertheless, it is even more important in this context.
213-217	19	Comment: It is desirable that the manufacturing process used for clinical batches of the biosimilar product should represent the production process of batches to become commercialised in the future. In the case when a production process optimisation is needed when clinical investigations phase has already been started, the guideline states that additional bridging data should be presented together with appropriate justification. Since this recommendation is issued in the context of quality, preferably the range of bridging data to be generated could solely consist of thorough physicochemical comparability exercises with no need of *in vivo* or clinical bridging studies. It would be very useful if the range of such bridging data would be	No. The extent of comparability exercise will depend on the type of the change.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		defined in this guideline.	
214	3	Comment: It is recognised that the scale and site for any given product may not be the same as that used to manufacture the clinical supply yet it is clear that it is still importance to use the same process that will be used when the product is approved for commercialisation. Proposed change: Consider amending the text as follows: 'However, it is recommended to generate the clinical data required for the comparability study with the test product derived from the ~~final~~ same manufacturing process and therefore representing the quality profile of the batches to become commercialised.	The revised text will speak about the "commercial" manufacturing process which is in line with the overarching quality guideline.
214-216	1	Comment: BIO recognizes that the scale and site for any given product may not be the same as that used to manufacture the clinical supply, yet it is essential to use the same process that will be employed when the product is approved for commercialization. Proposed change: "However, it is recommended to generate the clinical data required for the comparability study with the test product derived from the ~~final~~ same manufacturing process and therefore representing the quality profile of the batches to become commercialised."	The revised text will speak about the "commercial" manufacturing process which is in line with the overarching quality guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
214-217	18	'However, it is recommended to generate the clinical data required for the comparability study with the test product derived from the final manufacturing process and therefore representing the quality profile of the batches to become commercialised. Any deviation from this recommendation should be justified and supported by adequate additional bridging data.' We strongly support this recommendation	The revised text will speak about the "commercial" manufacturing process which is in line with the overarching quality guideline.
216-217	15	Comment: We propose to add the sentences in red as follows Proposed change: Any deviation from this recommendation should be justified and supported by adequate additional bridging data, according to EMA guidelines for changes introduced in the manufacturing process ("NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL / BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS -CPMP/ICH/5721/03").	The text has been modified.
218-221	1	Comment: BIO believes that a stepwise approach is desirable in biosimilar development.	No, there may be situations where the PK/PD studies may comprise a substudy within the larger safety and efficacy study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The clinical comparability exercise is ~~normally~~ a stepwise procedure that should begin with pharmacokinetic (PK) and~~, if feasible,~~ pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s)..."	
218-221	2	Comment: If the analytical and non-clinical comparability exercises indicate a high degree of similarity, it may be acceptable to conduct the clinical studies in parallel rather than in a stepwise manner beginning by pharmacokinetic studies followed by confirmatory efficacy and safety studies. As in new drug developments, these studies should not be considered as phases of development but rather as studies that address different components of the comparability exercise, since the purpose of the clinical programme for biosimilars is NOT to re-establish efficacy and safety, but to demonstrate similarity. Pharmacokinetic studies may be of a size comparable to that of efficacy studies, and would represent a similar level of risk to subjects and patients enrolled. We therefore propose wording that places less emphasis on the sequential nature of the studies. **Proposed change:** The clinical comparability exercise is normally	No. The conduct of PK studies separately before larger efficacy-safety studies has clear advantages. Additional PK studies may be needed during the efficacy-safety study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		comprises a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamics (PD) studies, and efficacy and safety trials or, in certain cases confirmatory PK/PD studies for demonstrating clinical comparability. These studies may generally be conducted in a stepwise manner.	
218-221	4	Comment: Since PD assessment (if possible for the specific product class) can be a surrogate for 'efficacy', are separate 'comparative efficacy' studies required?	In this case, the surrogate would replace the conventional clinical endpoint(s) but the study still addresses efficacy and safety.
218-221	8	Comment: As indicated in more details above (see general comments on Stepwise Approach), we consider that a stepwise approach is always desirable in biosimilar development Proposed change: Consider amending the text as follows: 'The clinical comparability exercise is ~~normally~~ a stepwise procedure that should preferably begin with pharmacokinetic (PK) and, ~~if feasible~~, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s). ~~or, in~~ In certain cases, confirmatory PK / PD studies for demonstrating clinical comparability may be possible but must be followed by clinical safety trials unless otherwise justified.'	No. There are exceptions to the stepwise conduct, especially when single dose studies are not feasible or possible. Clinical comparability includes both efficacy and safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
218-221	10	Comment: If the analytical and non-clinical comparability exercise indicate a high degree of similarity, it may be acceptable to conduct the clinical studies in parallel rather than in a stepwise manner beginning by pharmacokinetic studies followed by confirmatory efficacy and safety studies. As in new drug developments, these studies should not be considered as phases of development but rather as studies that address different components of the comparability exercise, since the purpose of the clinical programme for biosimilars is NOT to re-establish efficacy and safety, but to demonstrate similarity. Pharmacokinetic studies may be of a size comparable to that of efficacy studies, and would represent a similar level of risk to subjects and patients enrolled. We therefore propose a wording that places less emphasis on the sequential nature of the studies. Proposed change: The clinical comparability exercise normally comprises pharmacokinetic, and if feasible pharmacodynamic, studies, and efficacy and safety trials, or in certain cases confirmatory PK/PD studies for demonstrating clinical comparability. These studies will generally be conducted in a stepwise manner.	No. The conduct of PK studies separately before larger efficacy-safety studies has clear advantages. Additional PK studies may be needed during the efficacy-safety study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
218-221	14	Comment: As indicated in more details above (see general comments on Stepwise Approach), we consider that a stepwise approach is always desirable in biosimilar development Proposed change: The clinical comparability exercise is ~~normally~~ a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical comparability.	No. There are exceptions to the stepwise conduct, especially when single dose studies are not feasible or possible.
218-221	17	Comment: Here it may be emphasised that comparative efficacy data are needed but the amount of data needed may vary from none (efficacy is deduced from comparative data on physicochemical and biological characteristics, including a complete functional assessment), comparative PK studies , comparative PK/PD, a limited clinical trial (e.g. based on biomarkers) up to a full blown RCT. The company should justify their data package with respect to efficacy. Proposed change:	No. The current text allows the flexibility in the demonstration of efficacy and safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~The clinical comparability exercise is normally a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical comparability.~~ The clinical comparability exercise should address both efficacy and safety. For efficacy a stepwise procedure is recommended that may range from pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, or combined PK / PD studies, small clinical efficacy trial(s) or full-blown RCT. It may even be possible when justified to deduce clinical efficacy from comparative data of physicochemical and biological characteristics, including a complete functional assessment. The applicant needs to justify their data package with respect to efficacy.	
218-221	20	Comment: ("The clinical comparability exercise is normally a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK/PD studies for demonstrating clinical comparability."): We agree with the Draft Guideline's	No. There are situations when the normal sequence is not feasible, especially when the single dose studies are not possible and the PK/PD can be conducted as part of the efficacy-safety study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		requirement of a step-wise approach. We suggest that the final guideline make explicit the burden on the biosimilar applicant, before each next step, to identify and assess any observed difference between its proposed biosimilar and the reference product – and to consider remaining risks that other differences between the two products go undetected.	
232	18	Should the detailed guidance on PK in the MAbs guidance also be referenced here?	This GL gives general guidance whereas the purpose of the product class-specific GL is to give more detailed guidance. The revised GL refers to the biosimilar GLs on the EMA website.
233-234	16	In the absence of accepted criteria for similarity, a PK comparison does not make sense at all. There is no scientific basis for using the margins for small molecules. Proposed change: delete the need for comparative PK	No. The purpose of the PK studies is to demonstrate comparable exposure. The margins of the small molecules are not scientifically based either but seem to be practical.
233-236	1	Comment: BIO believes that criteria used in standard bioequivalence studies for chemically-derived products are generally not directly applicable to biological products. BIO also believes that the term "comparability limits" should be defined or referenced to provide greater clarity. Proposed change:	No. The current text seems to cover the essential information.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"While ~~T~~the criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, orally administered products may be acceptable in the absence of specific criteria for biologicals, they are generally not directly applicable. ~~Nevertheless~~ Therefore, the comparability limits for the main PK parameters should be defined and justified prior to conducting the study."	
233-236	7	Comment: Add a reference to the bioequivalence guideline Proposed change: The criteria used in standard clinical bioequivalence studies, (80-125)	No. There is a reference to the bioequivalence GL but the equivalence range must be justified in each case.
233-236	10	Comment: Referring to "Nevertheless, the comparability limits for the main PK parameters should be defined and justified prior to conducting the study." The term "comparability limits" should be defined or referenced to a possible statistical guidance, currently the term lacks clarity. Proposed change: "Nevertheless, the comparability limits for the main PK parameters in line with the ***Guideline on the investigation of bioequivalence*** (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) should be	No. The reference is given in the previous paragraph.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		defined and justified prior to conducting the study."	
233-236	15	Comment: We suggest the following revision Proposed change: "The criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, orally administered products are generally not directly applicable to biological. Therefore the comparability limits for the main PK parameters should be defined and justified prior to conducting the study."	No. The current text corresponds to the current experience and knowledge.
233-236	17	Line 233 -236 Comment: These lines are logical inconsistent: First the criteria for clinical bioequivalence studies are considered acceptable and then they should be defined an justified. Proposed change: Decided for on or the other. Preferred is: ~~The criteria used in standard clinical bioequivalence studies, initially developed for chemically derived, 233 orally administered products may be acceptable in the absence of specific criteria for biologicals. 234 Nevertheless, the comparability limits for the main PK parameters should be defined and justified prior 235 to conducting the study.~~	No. There is no inconsistency, see Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004) for the suitability of the standard bioequivalence study design and PK endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The comparability limits for the main PK parameters should be defined and justified prior conducting the study, this includes a justification when standard criteria for bioequivalence studies are chosen.	
235-236	4	Comment: Please provide clarification if the Agency recommends that justification is done in document for record and inclusion in the MA dossier or in a discussion with the Agency?	The justifications for the selected bioequivalence/comparability range and study design should be made according to guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004). The Applicant can always seek for scientific advice in the absence of clear guidance.
237-238	1	Comment: BIO believes the most sensitive test model should be used for demonstration of comparable pharmacokinetics. Proposed change: "For the demonstration of comparable pharmacokinetics, ~~it is advisable to select~~ the most sensitive test model should be selected.	No. The use of the most sensitive model may not always be possible or feasible.
237-238	4	Comment: If a given product is being developed for presentation in two different strengths/concentrations, would a demonstration of comparable pharmacokinetics be required for both strengths, or can that be inferred via extrapolation? Please clarify.	The text has been modified. Extrapolation depends of the PK of the reference product. PK can be extrapolated if the comparison has been performed within the linear part of the dose-exposure.
237-238	8	Comment:	No. The use of the most sensitive model may not always be possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest amending the text as follows: Proposed change: Consider amending the text as follows: 'For the demonstration of comparable pharmacokinetics, ~~it is advisable to select~~ the most sensitive test model should be selected.'	
237-238	14	Proposed change: "For the demonstration of comparable pharmacokinetics, ~~it is advisable to select~~ the most sensitive test model should be selected."	No. The use of the most sensitive model may not always be possible.
237-238	16	Why do you need the most sensitive model if there are acceptance criteria for comparison? Proposed change: delete	No. Usually, the appropriate acceptance criteria will depend on the model. The selected model should not have a high variability due to confounding factors. Nevertheless, a requirement of a "most sensitive model" may not always be possible or feasible.
237-244	6	Comment: It is not clearly stated that beside sensitivity also homogeneity plays a crucial role in selecting the appropriate study population for PK trial. It is recommended to revise the wording to comply with the most recent version of the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*). Proposed change:	The text is modified. The model should be sensitive to detect differences. Usuallly, this means a homogenous population.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For the demonstration of comparable pharmacokinetics, it is advisable to select a sufficiently sensitive and homogeneous test model. This is expected to reduce variability, and thus the sample size needed to prove equivalence, and can simplify interpretation. Healthy volunteers lack co-morbidity and co-medications and are likely to have less target-mediated clearance compared to patients. A single dose cross-over study with full characterisation of the PK profile, including the late elimination phase, is preferable. A parallel group design may be necessary with substances with a long half life and high risk of immunogenicity. PK studies are not always possible or feasible in healthy volunteers. In this case, the PK needs to be studied in patients. The most sensitive and homogeneous model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.	
237-244	20	Comment: ("For the demonstration of comparable pharmacokinetics, it is advisable to select the most sensitive test model. Healthy volunteers lack co-morbidity and co-medications and are likely to have less target-mediated clearance compared to patients. A single dose cross-over study with full characterisation of the PK profile, including the late	No. The purpose of the PK studies is to compare the PK profile and exposure. Demonstration of comparability in one sensitive population is sufficient. The term "most sensitive" is not used in the revised GL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		elimination phase, is preferable. A parallel group design may be necessary with substances with a long half life and high risk of immunogenicity.")): We agree with the Draft Guideline's statement that an applicant should demonstrate comparable pharmacokinetics by selecting "the most sensitive test model," although we suggest that the final guideline indicate applicants "should" select the most sensitive test model – instead of merely describing this as "advisable." For biologics such as monoclonal antibodies, specific regions of the molecule may be involved in different mechanisms of action in different indications. Accordingly, it may not be possible to define only one indication as most sensitive. In this case, clinical testing may be needed in more than one indication. We also recommend that the final guideline note that, in some cases, identifying a single "most sensitive" indication or patient population for testing purposes will not be possible. Two or more patient populations may be sensitive for different reasons: one might be more sensitive for detecting differences in safety, and the other more sensitive for detecting differences in effectiveness, immunogenicity, or pharmacokinetics. We suggest that the final guideline state that an applicant should consider whether testing in more than one condition of use and/or patient population is warranted.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
238-239	16	But patients show more variability so you may need large numbers to show differences. Proposed change: leave the choice volunteers or patients to the company	The Applicant can use any model that is sensitive enough to demonstrate comparable PK.
238-244	14	Comment: It would improve understanding if examples could be included to illustrate when PK studies in healthy volunteers could be acceptable, given the nature of the biological drug effect.	The issue is obviously the safety. The Applicant has to justify the use of healthy volunteers to national competent authorities when seeking for clinical trial authorisation.
240-241	8	**Comment**: It should also be mentioned that a steady state design may be needed for products with a long half life. **Proposed change**: Consider amending the text as follows: ' A parallel group design may be necessary with substances with a long half life and/or high risk of immunogenicity. **Also, a steady state design should be considered for products with a long half life.'**	The text has been slightly modified: "A parallel group design may be necessary with substances with a long half-life and/**or** high risk of immunogenicity". Steady state kinetics is investigated in multiple dose studies. A long half-life is not an argument for the omission of the single dose study.
240-241	14	Comment: It should also be mentioned that a steady state design may be needed for products with a long half-life. Proposed change: A parallel group design may be necessary with substances with a long half-life and	See the previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		high risk of immunogenicity. Also, a steady state design may be needed for products with a long half-life.	
242-244	4	Comment: If the PK is tested in patients, then PK determination after a single dose would not be ethical; especially if the dosing regimen recommendation is multiple doses during the treatment period.	Agreed. The intention is not to perform single dose studies in patients. This is now clarified in the text. The GL explains that the PK studies may be modified when performed in patients on treatment. Steady state kinetics is investigated in multiple dose studies.
244	8	Comment: Referring to “The most sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.”, we suggest to slightly reword the sentence to recognize that patients must be used due to the nature of the biological drug effect. Proposed change: Consider amending the text as follows: ‘The clinically acceptable most sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.’	The acceptability of study in a sensitive test population depends on the safety which is assessed in the context of the clinical trial notification/authorisation.
242-244	10	Comment: Referring to “The most sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.”, we suggest to slightly reword the sentence to recognize	The acceptability of study in a sensitive test population depends on the safety which is assessed in the context of the clinical trial notification/authorisation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that patients must be used due to the nature of the biological drug effect. Proposed change: "The clinically acceptable most sensitive model population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored."	
242-244	14	Comment: Referring to "The most sensitive model/population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored.", we suggest to slightly reword the sentence to recognize that patients must be used due to the nature of the biological drug effect. Proposed change: "The clinically acceptable most sensitive model population, i.e. that has fewer factors that cause major inter-individual or time-dependent variation, should be explored."	The acceptability of study in a sensitive test population depends on the safety which is assessed in the context of the clinical trial notification/authorisation.
245-248	2	Comment: The way the section is worded, suggests that "confirmatory efficacy clinical trial(s)" will always be needed. However, as stated in lines 218-221, confirmatory PK/PD trials may also be sufficient in certain cases. Therefore, we suggest revising the	No, the wording "may be useful" does not imply that confirmatory efficacy studies are always required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		wording to allow for more flexibility in the clinical program. Proposed change: In certain cases, such as important target-mediated clearance, highly immunogenic proteins or highly variable PK parameters, it may be useful to collect additional PK data in a clinical setting within the confirmatory efficacy clinical trial(s) as it allows further investigation of clinical impact of variable pharmacokinetics and possible changes in PK over time.	
245-250	10	Comment: The way the section is worded, suggests that "confirmatory efficacy clinical trial(s)" will always be needed. However, as stated in lines 218-221, confirmatory PK/PD trials may also be sufficient in certain cases. Therefore, we suggest revising the wording to allow for more flexibility in the clinical program. **Proposed change:** In certain cases, such as important target-mediated clearance, highly immunogenic proteins or highly variable PK parameters, it may be useful to collect additional PK data in **a clinical setting** within the confirmatory efficacy clinical trial(s) as it allows further	No, the wording "may be useful" does not imply that confirmatory efficacy studies are always required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		investigation of clinical impact of variable pharmacokinetics and possible changes in PK over time.	
246-247	17	Comment: Please include the following: "…it may be useful to collect additional PK data within the safety/immunogenicity trail or a confirmatory efficacy clinical trial(s)U (when performed)…"	The text has been modified.
249-250	1	Comment: BIO believes the anti-drug antibodies discussion would benefit from a discussion of neutralizing versus non-neutralizing antibody formation. Proposed change: "Anti-drug antibodies should be measured in parallel to PK assessment using the most appropriate sampling time points. Studies of anti-drug antibodies should have adequate specificity and sensitivity to discern and quantify the existence of neutralizing vs. non-neutralizing antibodies."	No, there is separate guidance on the ADA testing strategy, including neutralising ADAs (EMEA/CHMP/BMWP/14327/2006).
249-250	8	Comment: Some rephrasing would be good as antibodies should be measured for all products, the current text seems to be limiting the requirement to highly immunogenic proteins.'	Agreed. The sentence has been transferred to the previous paragraph in order to avoid misunderstandings.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending the text as follows: 'Anti-drug antibodies should be measured for all biosimilars and reference products in parallel ~~to~~ via PK assessment using the most appropriate sampling time points.'	
249-250	8	Comment: Anti-drug antibodies discussion omits a discussion of neutralizing versus non-neutralizing antibody formation. Not all anti-drug antibodies are neutralizing. Proposed change: Consider adding the following text at the end of line 50: 'Where anti-drug antibodies are present, studies of anti-drug antibodies should have adequate specificity and sensitivity to discern and quantify the existence of neutralizing vs. non-neutralizing antibodies.'	No. There is special guidance on the ADA testing strategy (EMEA/CHMP/BMWP/14327/2006).
249-250	14	Comment: Anti-drug antibodies discussion omits a discussion of neutralizing versus non-neutralizing antibody formation. Not all anti-drug antibodies are neutralizing.	No. There is special guidance on the ADA testing strategy (EMEA/CHMP/BMWP/14327/2006).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please consider adding at the end of line 250: 'Where anti-drug antibodies are present, studies of anti-drug antibodies should have adequate specificity and sensitivity to discern and quantify the existence of neutralizing vs. non-neutralizing antibodies.'	
249-250	14	Comment: Anti-drug antibodies should be measured in parallel to PK assessment using the most appropriate sampling time points Some reordering would be good as antibodies should be measured for all products (as specified in 5.4). The current positioning in line 249/250 seems to be limiting the requirement to 'certain cases' as highly immunogenic proteins. Proposed change: Move the sentence "Anti-drug antibodies should always be measured in parallel to PK assessments using the most appropriate time points" to the end of the previous paragraph (line 244)	Agreed. The sentence has been transferred to the previous paragraph in order to avoid misunderstandings.
249-250	18	Anti-drug antibodies should be measured in parallel to PK assessment using the most appropriate sampling time points Some reordering would be good as antibodies should be measured for all products (as specified in 5.4). The	Agreed. The sentence has been transferred to the previous paragraph in order to avoid misunderstandings

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		current positioning in line 249/250 seems to be limiting the requirement to 'certain cases' as highly immunogenic proteins. Proposed change: Move the sentence "Anti-drug antibodies should always be measured in parallel to PK assessments using the most appropriate time points" to the end of the previous paragraph (line 244)	
251-252	8	Comment: We agree with the principle that for characterising PK processes s.c. administration is the more sensitive route and more likely to show differences between biosimilar and reference drug than i.v. It is therefore possible to waive the evaluation of i.v. administration if comparability in absorption and elimination has been demonstrated for the s.c. route, provided that: The biosimilar i.v. formulation and s.c. formulation have the same excipients. If this is not the case, data should be generated to understand the effect of the different formulations on PK. The biosimilar and the originator i.v. formulations have the same excipients. If this is not the case, PK data should be generated. We propose to add this clarification in the text. Proposed change:	The text has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Consider amending the text as follows: 'Thus, it is possible to waive the evaluation of intravenous administration if comparability in both absorption and elimination has been demonstrated for the subcutaneous route**. In order to waive the evaluation the formulations for the intravenous and subcutaneous dosage forms should be the same for each given product (although the biosimilar and reference product need not use the same formulation). If either the biosimilar product or the reference product use different formulations for intravenous and subcutaneous dosage forms, the ability to extrapolate comparable and elimination results to the intravenous formulation may be compromised and the routes of administration need to be tested separately.'**	
251-252	14	Comment: We agree with the principle that for characterising PK processes s.c. administration is the more sensitive route and more likely to show differences between biosimilar and reference drug than i.v. It should be considered that there may be different i.v. and s.c. formulations. This concept is not captured in the guidance. Proposed change:	The text has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Thus, it is possible to waive the evaluation of intravenous administration if comparability in both absorption and elimination has been demonstrated for the subcutaneous route, and if the route of administration of the biosimilar product includes the subcutaneous administration. In order to waive the evaluation the formulations for the reference product and the biosimilar must also be the same. If this is not the case, the route or formulations need to be tested separately.	
253-254	7	Comment: It would not be possible to waive the evaluation of IV administration if the molecule exhibited flip flop kinetics. It is assumed that this is not the case.	The text has been modified.
255-256	19	Comment: Current version of the Guideline indicates that in single dose PK studies, the primary parameters are the $AUC_{(0\text{-}inf)}$ for i.v. and $AUC_{(0\text{-}inf)}$ and usually C_{max} for s.c. administration. The basis for the need of inclusion of $AUC_{(0\text{-}inf)}$ as a primary PK parameter was not provided, while it is largely acceptable (e.g. by the *Guideline on the investigation of bioequivalence,* CPMP/EWP/QWP/1401/98 Rev. 1/Corr) to conclude on equivalence using other PK parameters, e.g. AUC(0-t). Providing of scientific basis for such primary end-point(s) selection together with allowance of the possibility of justification of AUC(0-t) evaluation as	$AUC_{0\text{-}inf}$ is required since the absorption does not affect the AUC after IV administration. The text has been modified: "measured and quantified as appropriate"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(one of) primary endpoint(s) would be highly appreciated.	
255-260	8	Comment: Similar to the bioequivalence guidance, the key PK parameters to demonstrate comparability of PK should be AUC $_{0\text{-inf}}$ and C_{max} following a single dose (as suggested). It is well reported that many biologics, especially monoclonal antibodies, exhibit 2-compartmental PK and therefore parameters such as Vdss and $T_{1/2}$ cannot be accurately estimated using noncompartmental analysis and do not add to the comparability exercise. Therefore, such additional parameters should not be suggested to be estimated in all cases, but only as appropriate. For many biologics exhibiting target mediated clearance, the variability of PK is often associated with the inter-individual differences in the target. Therefore the AUC following the first dose administration in a multiple dose study represents the least sensitive measure of AUCt. Therefore, we suggest that it be included as the secondary endpoint. Since AUC0-t at steady state represents AUC0-inf following a single dose, it is the appropriate primary endpoint (as suggested in the guidance) when a single dose study is not feasible. Proposed change:	It is argued that the AUC after first dose will better reflect absorption. The text concerning multiple dose studies and steady state kinetics has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Consider amending the text as follows: 'Secondary parameters such as tmax, volume of distribution, and half-life, should also be ~~estimated~~ measured and quantified as appropriate. In a multiple dose study, the primary parameters should be the ~~truncated AUC after the first administration until the second administration (AUC0-t) and~~ AUC over a dosage interval at steady state (AUC_T). Secondary parameters are Cmax and Ctrough at steady state and truncated AUC after the first administration until the second administration (AUC0-t)'	
255-260	10	Comment: Similar to the bioequivalence guidance, the key PK parameters to demonstrate comparability of PK should be AUC0-inf and Cmax following a single dose (as suggested). It is well reported that many biologics, especially monoclonal antibodies, exhibit 2-compartmental PK and therefore parameters such as Vdss and T1/2 cannot be accurately estimated using noncompartmental analysis and do not add to the comparability excercise. Therefore, such additional parameters should not be suggested to be estimated in all cases, but only as appropriate. For many biologics exhibiting target mediated clearance, the variability of PK is often associated with the inter-individual differences in the target. Therefore	The text concerning multiple dose studies has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the AUC following the first dose administration in a multiple dose study represents the least sensitive measure of AUCt. Therefore, we suggest that it be included as the secondary endpoint. Since AUC0-t at steady state represents AUC0-inf following a single dose, it is the appropriate primary endpoint (as suggested in the guidance) when a single dose study is not feasible. Proposed change: Secondary parameters such as tmax, volume of distribution, and half-life, should also be estimated as appropriate. In a multiple dose study, the primary parameters should be the ~~truncated AUC after the first administration until the second administration (AUC0-t) and~~ AUC over a dosage interval at steady state (AUC_{τ}). Secondary parameters are Cmax and Ctrough at steady state and truncated AUC after the first administration until the second administration (AUC0-t)"	
255-260	14	Comment: Similar to the bioequivalence guidance, the key PK parameters to demonstrate comparability of PK should be AUC0-inf and Cmax following a single dose (as suggested). It is well reported that many biologics, especially monoclonal antibodies, exhibit 2-compartmental PK and therefore parameters such as	The text concerning multiple dose studies has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Vdss and T1/2 cannot be accurately estimated using noncompartmental analysis and do not add to the comparability exercise. Therefore, such additional parameters should not be suggested to be estimated in all cases, but only as appropriate. For many biologics exhibiting target mediated clearance, the variability of PK is often associated with the inter-individual differences in the target. Therefore the AUC following the first dose administration in a multiple dose study represents the least sensitive measure of AUCt. Therefore, we suggest that it be included as the secondary endpoint. Since AUC0-t at steady state represents AUC0-inf following a single dose, it is the appropriate primary endpoint (as suggested in the guidance) when a single dose study is not feasible. Proposed change: Secondary parameters such as tmax, volume of distribution, and half-life, should also be ~~estimated~~ measured and quantified as appropriate. In a multiple dose study, the primary parameters should be the ~~truncated AUC after the first administration until the second administration (AUC0-t) and~~ AUC over a dosage interval at steady state (AUC_T). Secondary parameters are Cmax and Ctrough at steady state and truncated AUC after the first	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		administration until the second administration (AUC0-t)"	
255-260	14	**Comment:** BIO believes secondary parameters should also be measured and quantified. **Proposed change:** "Secondary parameters such as t_{max}, volume of distribution, and half-life, should also be ~~estimated~~ measured and quantified."	The text has been modified.
256-257	1	**Comment:** BIO believes secondary parameters should also be measured and quantified. **Proposed change:** "Secondary parameters such as t_{max}, volume of distribution, and half-life, should also be **measured and quantified."**	The text has been modified.
256-257	15	**Comment:** We suggest the following revision **Proposed change:** "Secondary parameters such as t_{max}, volume of distribution, and half-life, should also be **measured and quantified**".	The text has been modified.
262-282	10	Comment: It is stated that in certain cases comparative PK/PD studies may be sufficient to demonstrate clinical comparability, provided that certain conditions are	No. It is expected that the PD parameters used in efficacy studies have to be accepted surrogates for efficacy. With regard to the dose response, the text has been modified: "A clear dose-response or a concentration-response relationship has been demonstrated."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		fulfilled. We highly appreciate this approach and would like to clarify the meaning of “clinical relevance” in line 263. In particular, the PD marker does not necessarily have to be a surrogate for efficacy, but could also be a parameter describing the pharmacological effect of the molecule. Furthermore, in some cases a time-course of the PK/PD profile may provide the information required to inform about a concentration-response relationship and may not require separate doses to be investigated. Proposed change: Line 263: The PD markers should be selected on the basis of their clinical or **pharmacological** relevance. Line 268: A clear dose-response **or a concentration-response** relationship has been demonstrated.	
262-263	2	Comment: It is stated that in certain cases comparative PK/PD studies may be sufficient to demonstrate clinical comparability, provided that certain conditions are fulfilled. We highly appreciate this approach and would like to clarify the meaning of “clinical relevance” in line 263. In particular, the PD marker does not necessarily have to be a surrogate for efficacy, but could also be a	See above. No. It is expected that the PD parameters used in efficacy studies have to be accepted surrogates for efficacy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		parameter describing the pharmacological effect of the molecule. Therefore, we would like to suggest to include the "pharmacological" relevance as well. **Proposed change:** The PD markers should be selected on the basis of their clinical or pharmacological relevance.	
262-263	8	Comment: In the current guideline it is specified that for the PD studies the selected dose should be in the steep part of the dose-response curve and that more than one dose level may be useful. This information should be kept in the revised document. Proposed change: Consider amending the text as follows: 'It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies whenever feasible. The PD markers should be selected on the basis of their clinical relevance. The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful.'	No, the issue of multiple doses is discussed later in the chapter.
262-263	8	Comment:	No, the use of more than one PD marker is a logical approach when no established surrogate marker is available but other,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		While we agree that in some specific cases comparative PK/PD studies may be appropriate to demonstrate comparable efficacy, as indicated in more detail above (see General Comment on PD fingerprinting concept), we do not consider that this is a useful or helpful concept for this guidance for un-validated PD markers, as it should only be considered on a case-by-case basis depending upon the number of relevant PD markers and the structural and functional complexity of the molecule in question and not as an principle for biosimilarity. It is unacceptable to justify that multiple surrogate PD markers/biomarkers would be more valid or sound if none of these multiple markers is an accepted one. Non-proven, shaky or scanty biomarkers will not suddenly prove more reliable when used in combination. In addition, for clarity also consider proving additional detail regarding other factors that need to be considered for these studies. We suggest that the EMA should either omit reference to this concept or if it remains provide additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy. Proposed change:	pharmacologically relevant PD markers exist. Nevertheless, the GL recommend a discussion with regulatory authorities before embarking on such studies in order to discuss critical matters, including the acceptance ranges and safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Consider amending the text as follows: 'It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies whenever feasible. The PD markers should be selected on the basis of their clinical relevance. ~~Normally,~~ Comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate ~~clinical comparability~~ comparable efficacy, provided that all the following conditions are met: • A clear dose-response relationship has been demonstrated. If not, the recommended study design is to conduct a multiple dose-exposure-response study. This design would ensure that the biosimilar and the reference can be compared within the linear ascending part of the dose-response curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be sensitive but it cannot replace comparative studies. **Patient-related factors such as differences in co-morbidities and co-medications may exist.** • The selected PD marker/biomarker is an accepted surrogate marker ~~and can be related~~ **that is correlated** to patient outcome to the	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, euglycaemic clamp test to compare two insulins, ad magnetic resonance imaging of disease lesions to compare two ß-interferons. **In this situation, the applicant should consider clinical safety and immunogenicity as distinct matters in the establishment of overall clinical similarity as described in Section 5.4.** ~~The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of surrogacy is very rare. In such cases, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability.'~~	
262-282	14	Comment: We appreciate the proposed approach and propose to further clarify the meaning of "clinical relevance" in line 263. In particular, the PD marker does not necessarily have to be a surrogate for efficacy, but	No, the use of more than one PD marker is a logical approach when no established surrogate marker is available. Nevertheless, the GL recommends a discussion with regulatory authorities before embarking on such studies in order to discuss critical matters, including the acceptance

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		could also be a parameter describing the pharmacological effect of the molecule. Furthermore, in some cases a time-course of the PK/PD profile may provide the information required to inform about a concentration-response relationship and may not require separate doses to be investigated. We do not consider PD fingerprinting concept a useful or helpful concept for this guidance for un-validated PD markers, as it should only be considered on a case-by-case basis depending upon the number of relevant PD markers and the structural and functional complexity of the molecule in question and not as an overarching principle for biosimilarity. We suggest that the EMA should either omit reference to this concept or if it remains provide additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy. In addition, 'accepted' (biomarker) implies that the biomarker has been validated, qualified and accepted according to EU guidance on biomarkers. We propose to reword as 'suitable biomarker'. Proposed change:	ranges and safety.

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		Consider amending the text as follows: 'It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies whenever feasible. The PD markers should be selected on the basis of their clinical relevance. ~~Normally,~~ Comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate ~~clinical comparability~~ comparable efficacy, provided that all the following conditions are met: • A clear dose-response relationship has been demonstrated. If not, the recommended study design is to conduct a multiple dose-exposure-response study. This design would ensure that the biosimilar and the reference can be compared within the linear ascending part of the dose-response curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be sensitive but it cannot replace comparative studies. **Patient-related factors such as differences in co-morbidities and co-medications may exist.** • The selected PD marker/biomarker is an accepted surrogate marker ~~and can be related~~ **that is correlated** to patient outcome to the	

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		extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, euglycaemic clamp test to compare two insulins, ad magnetic resonance imaging of disease lesions to compare two ß-interferons. **In this situation, the applicant should consider clinical safety and immunogenicity as distinct matters in the establishment of overall clinical similarity as described in Section 5.4.** ~~The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of surrogacy is very rare. In such cases, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability.'~~	
262-282	18	We appreciate the proposed approach and propose to further clarify the meaning of "clinical relevance" in line 263. In particular, the PD marker does not necessarily have to be a surrogate for efficacy, but could also be a parameter describing the	It is clear without mentioning that the PD markers should be appropriate. There are PD markers that are generally accepted but never formally validated. The use of a combination of PD markers that are selected based on their pharmacological relevance is a new concept. Therefore, the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacological effect of the molecule. Furthermore, in some cases a time-course of the PK/PD profile may provide the information required to inform about a concentration-response relationship and may not require separate doses to be investigated. We do not consider PD fingerprinting concept a useful or helpful concept for this guidance for un-validated PD markers, as it should only be considered on a case-by-case basis depending upon the number of relevant PD markers and the structural and functional complexity of the molecule in question and not as an overarching principle for biosimilarity. We suggest that the EMA should either omit reference to this concept or if it remains provide additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy. In addition, 'accepted' (biomarker) implies that the biomarker has been validated, qualified and accepted according to EU guidance on biomarkers. We propose to reword as 'suitable biomarker'. Proposed change: Consider amending the text as follows: It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies	GL recommend a discussion with regulatory authorities before embarking on such studies in order to discuss critical matters, including the acceptance ranges.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		whenever feasible. The PD markers should be selected on the basis of their clinical or pharmacological relevance. ~~Normally,~~ Comparative efficacy trials are required for the demonstration of ~~clinical comparability~~comparable efficacy. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met: • A clear dose-response or a concentration-response relationship has been demonstrated. If not, the recommended study design is to conduct a multiple dose-exposure-response study. This design would ensure that the biosimilar and the reference can be compared within the linear ascending part of the dose-response curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be sensitive but it cannot replace comparative studies. • The selected PD marker/biomarker is ~~an accepted~~a suitable surrogate marker and ~~can be~~that is correlated to patient outcome to the extent that demonstration of similar effect on	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, euglycaemic clamp test to compare two insulins, ad magnetic resonance imaging of disease lesions to compare two ß-interferons. Add the following proposed text: 'In cases where comparative pharmacodynamic studies are claimed to be most suitable to provide the pivotal evidence for similar efficacy, applicants should also provide sufficient reassurance of clinical safety, particularly immunogenicity as described in Section 5.4. Change 'combination of markers' to 'combination of appropriate markers'. The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of surrogacy is very rare. In such cases, a combination of appropriate markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		evidence to conclude on clinical comparability.	
263	15	Comment: We suggest the following revision Proposed change: The PD markers should be selected on the basis of their clinical or pharmacological relevance	No, the selected PD markers should have correlation to efficacy.
263	16	This is in contradiction with lines 279-280 where it says that there are no validated PD markers Proposed change: delete	No. There are validated, generally accepted and plausible PD markers. The first two may be used as surrogates.
264-278	2	Comment: It is stated that in certain cases comparative PK/PD studies may be sufficient to demonstrate clinical comparability, provided that certain conditions are fulfilled. This progressive approach of the CHMP is appreciated by EBG. The biosimilar concept is applied on a case-by-case basis, and as such the comparability program consisting of quality, non-clinical and clinical studies is specifically adapted to each biosimilar development in order to adequately demonstrate similar quality, safety and efficacy. In specific circumstances clinical efficacy and safety studies may not be necessarily part of the clinical comparability programme as is also discussed in the current draft overarching guideline. To support this approach it has	No. There are validated, generally accepted and plausible/scientifically relevant PD markers. The first two may be used as surrogates for efficacy.

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		to be emphasized that the spectrum of the available tools for physico-chemical characterization are rapidly evolving, and comparative methods to address the biological activity of the biosimilar and the reference biological medicinal products are available. In cases when appropriately sensitive primary clinical endpoints are not available for the demonstration of comparative efficacy, relevant and sensitive PD data with appropriately defined equivalence margins, in principle, may also provide already pivotal information for the biosimilarity exercise. Therefore the specific circumstance for the omission of comparative clinical efficacy and/or safety studies, i.e. when PK and/or PD data would be sufficient, should be justified case-by-case and should also rely on the scientific data provided in the physico-chemical and non-clinical data package. Furthermore, in some cases a time-course of the PK/PD profile may provide the information required to inform about a concentration-response relationship and may not require separate doses to be investigated. Proposed change: Line 268: A clear dose-response or a concentration-response relationship has been demonstrated. Line 273-275: The selected PD marker/biomarker is an accepted or scientifically justified sensitive surrogate	

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		marker reflecting the biologic effect(s) of the compound to an extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome.	
264-267	1	Comment: BIO's long-standing view, based on the current state of scientific knowledge concerning biotechnology products, is that clinical studies beyond pharmacokinetic/pharmacodynamic (PK/PD) studies are essential for the evaluation of safety and effectiveness for biosimilar products. This is because minor changes made by a manufacturer to starting materials or to manufacturing processes can lead to changes in the product that may not be detectable by any other means Proposed change: "Normally, comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product may ~~be sufficient to demonstrate~~ inform clinical comparability, provided that all the following conditions are met:"	No. The use of validated or generally accepted surrogate markers is possible to demonstrate clinical comparability in an appropriate clinical study.
264-267	7	Comment: An additional paragraph is needed about the criterion that will be used to demonstrate PD comparability, particularly if this is planned to be used to	The applicant is expected to justify the use of a PD marker. The selection of the equivalence ranges for PD markers is dependent on their correlation to the clinical efficacy endpoints as well as on the size of the effect of the reference

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		demonstrate clinical comparability. For example, will the standard BE criteria be used to demonstrate comparability? The PD criteria for comparability should be pre-specified and justified.	product compared to the smallest clinically meaningful change in a particular clinical endpoint. At the moment, no general guidance can be given on this topic.
264-267	17	Comment: As a rule the biosimilar should be so highly similar that comparability does not need to be confirmed by comparative efficacy trials. Therefore, it should not be stated that normally comparative efficacy trials are needed. On the other hand, a confirmatory comparative efficacy may be the only possibility to confirm efficacy clinically when there is a lack of suitable PD parameters. Proposed change: ~~Normally, comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, c~~Comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:	No. The original text highlights the fact that surrogate PD markers rarely exist. It remains to be demonstrated that the improvement of physico-chemical and structural analytics will make it possible to conclude biosimilarity alone.
264-267 273-275	20	Comment: ("Normally, comparative efficacy trials are required for the demonstration of clinical comparability. In certain cases, however, comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate clinical comparability,	The improvement of the physico-chemical testing methods and increasing understanding of structure-function relationship may gradually loosen the requirements of large clinical trials to demonstrate comparable efficacy and safety. The original text reflects the current state of the regulatory requirements after several years since the approval of the

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		provided that all the following conditions are met … The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome.") : We commend the Draft Guideline's use of "normally" to establish a presumption in favor of clinical efficacy trials to establish biosimilarity. We suggest that the final guideline specify that similar efficacy should be demonstrated using clinically meaningful endpoints in adequately powered, randomized, parallel group comparative clinical trials, with equivalence margins. We also suggest that the final guideline establish a higher standard for acceptable pharmacodynamic markers. Due to the complexity of biological products, two very similar molecules may have similar effects on some outcomes, but differing effects on others. These differing effects may depend, for example, on different parts of the molecule, the relative abilities of the molecules to penetrate different tissues, and whether the molecules can be administered chronically without immunogenicity. An applicant should be required to conduct a clinical efficacy trial unless highly sensitive pharmacodynamic studies provide a convincing demonstration of clinical comparability. Moreover, an applicant should show a	first biosimilars and after tens of scientific advices. Nevertheless, the text will allow a more flexible approach when the concept of biosimilarity will evolve.

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		"compelling scientific basis" for concluding that an endpoint will be "predictive of the standard, meaningful clinical endpoint," rather than merely "ensur[ing] a similar effect on the clinical outcome." In these cases, the CHMP should require applicants to gather data on the standard endpoint after approval. If gathering confirmatory data would not be feasible, the product should not be approved on the basis of the non-standard endpoint.	
268	8	Comment: We consider that in some cases a time-course of the PK/PD profile may provide the information required to inform about a concentration-response relationship and may not require separate doses to be investigated. Proposed change: Consider amending text as follows: 'A clear dose-response or a concentration-response relationship has been demonstrated.	The text has been modified accordingly.
268	15	Comment: We suggest the following revision Proposed change: A clear dose-response or a concentration- response relationship has been demonstrated.	The text has been modified accordingly.
268	19	Comment:	The text "clear dose response has been demonstrated" means

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		It is suggested that the Agency defines if clear dose-response relationship may be proven on the basis of extensive literature data (if available for given product) and/or Applicant's in vitro studies results.	that it is possible to conclude the dose-response relationship of the reference product by using appropriate published information. This may make it possible to compare the test and the reference only at one dose level.
268-272	17	Comment: It could be added that if PK-PD studies can be conducted in healthy volunteers, suboptimal clinical doses may be used for PK-PD characterisation to achieve a dose response in the linear part of the curve. Proposed change: Please, add information on the suitability of suboptimal clinical doses.	Agreed. This information has been added to the PK chapter.
269	14	Comment: It would be helpful to provide more specificity regarding the design of the multiple dose – exposure – response study. In particular, how many doses would be needed? Proposed change: Please expand on the design of the dose – response study.	The experience of such studies is still very limited. The goal is to demonstrate the sensitivity of the selected dose(s) to find differences between the test and the reference. The applicant has to justify the study design and the selected dose levels.
272	15	Comment: We suggest to add the sentences in red as follows Proposed change:	No. These issues are discussed in the context of efficacy and safety.

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		"Patient-related factors such as differences in co-morbidities and co-medications may exist. In particular the competency of the immune system needs to be taken into account, since some diseases or medications are known to result in immune suppression."	
279	16	I assume disease lesions in MS are meant. Proposed change: add MS	Yes. This is now clarified in the text.
273-282	14	Comment: We propose in this section to add clarifying text regarding the fact that, depending on the product, it may become more difficult to choose the best PD marker as uncertainty about the mechanism of action increases, specifically when different components contribute to the mechanism of action. Certainty/uncertainty about the mechanism of action needs to be explicitly addressed in the justification of the suitability of the selected PD marker. Proposed change: "….may provide sufficient evidence to conclude on clinical comparability. Knowledge on the mechanism of action (including its degree of certainty) should be explicitly addressed by the sponsor on a case by case basis."	No. The choice of the PD-marker depends on its ability to reflect the clinical effect.
279	17	*"…. and magnetic resonance imaging of disease*	It is true that MRI-derived endpoints are not recommended as

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		lesions to compare two β-interferons. " Comment: This is incorrect MRI is not a surrogate marker for clinical efficacy in multiple sclerosis. It is a marker of biological activity and accepted as endpoint in biosimilar exercises for betaferons. Stating here that MRI has be accepted as surrogate marker for efficacy could be used to define MRI as primary endpoint for any multiple sclerosis product including products with new mechanism of action. It is proposed to move this sentence to another place. Proposed change: The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. Relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons and euglycaemic clamp test to compare two insulins. ~~, and magnetic resonance imaging of disease lesions to compare two beta/interferons.~~ The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation	primary efficacy endpoints in the development of new innovative medicinal products for the treatment of MS. The text has been modified to make clear that MRI is acceptable for the comparison of two beta interferons.

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		of surrogacy is very rare. In such cases, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude on clinical comparability. As an example magnetic resonance imaging has been accepted as marker of biologicval activity to compare two beta-interferons.	
279-280	7	Comment: It is difficult to justify without head to head comparison if the evidence is scanty.	This paragraph deals with the use of multiple PD-markers. It is expected that regulatory authorities are consulted before embarking on a study that should compare the test and the reference.
279-282	2	Comment: In some cases where only a weakly validated PD marker is available, but safety is associated with and/or reflected by the given marker as well, a combination of such information can also be used to conclude on clinical comparability. Proposed change: The evidence for a surrogacy of a PD marker/biomarker is often scanty and formal validation of surrogacy is very rare. In such cases, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, or safety data associated with, or reflected by, the given marker, may provide sufficient evidence to conclude on clinical comparability.	No, the current text reflects the current stage of knowledge.

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279-282	16	That is a remarkable statement missing any scientific basis. Combining insufficient information does not increase reliability of the data. Maybe only in the case that the PD markers are completely independent biologic activities, which is hardly ever the case. Proposed change: delete	It is expected that the prosed PD markers will be scientifically plausible- the use of orthogonal tests will add to the evidence for comparability. However, the Applicants are advised to discuss this approach with regulatory authorities upfront to solve the scientific problems of this approach, if possible.
280-282	1	Comment: BIO recommends caution when interpreting that multiple surrogate PD markers/biomarkers would be more valid or sound than a single nonvalidated marker, if none of these multiple markers are themselves validated/accepted. Also BIO believes that examples (as offered in Lines 275-278) of the “sound pharmacological principles” that “may provide sufficient evidence to conclude on clinical comparability” would benefit the utility of the guideline. Proposed change: BIO suggests that EMA either omit reference to this concept, or if it remains, provide additional discussion explaining its limitations and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy.	It is expected that the prosed PD markers will be scientifically plausible- the use of orthogonal tests will add to the evidence for comparability. However, the Applicants are advised to discuss this approach with regulatory authorities upfront. For time being, there is no experience on the multiple PD marker approach. Therefore, the decision on its approvability is made on case by case.
280-282	15	Comment:	The appropriateness is judged by the regulatory authorities

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		We suggest the following revision Proposed change: In such cases, a combination of appropriate markers selected based on sound	on case by case basis.
282	14	Comment: This section 5.2 or the specific section 6 should also address how extrapolation would be handled if comparable efficacy is demonstrated on the basis of a PK-PD study only and if and how the need or wish to extrapolate would affect the design and parameter choice for a PK-PD study as described in the previous lines. Likewise, the applicant would have to consider if a PK-PD study would provide sufficient information on safety and immunogenicity in the extrapolated indications. Depending on the chosen approach, a reference to Section 6 should be included. Proposed change: See above, no wording proposed	This approach is possible only if the physicochemical and structural analyses will demonstrate very high degree of comparability. It is expected that the prosed PD markers will be scientifically plausible. Using orthogonal tests will further add to the evidence for comparability. However, the Applicants are advised to discuss this approach with regulatory authorities upfront, including its impact on extrapolation. For time being, there is no experience on the multiple non-PD marker approach and extrapolation. Therefore, the decision on its approvability, including extrapolation, is made on case by case.
283-285	16	This is unacceptable. Positions of the regulatory agencies should be transparent and open for public and scientific scrutiny. The possible biosimilar applications concern a limited number of products. The CHMP should publish a list of products with acceptable markers and equivalence margins **Proposed change:**	Biosimilarity is an evolving concept that is maturing along with increasing understanding of the structure-function relationship, improving analytical methodology, and increasing experience of the current biosimilars. The authorities cannot obstruct drug development because of uncertainty and lack of previous studies on novel approaches. However, the burden of evidence is on Applicants. In this

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		add list and equivalence margins	case, a cautious approach is applied by the regulators. It is expected that the prosed PD markers will be scientifically plausible and that the use of orthogonal tests will add to the evidence for comparability. In addition, the Applicants are advised to discuss this approach with regulatory authorities upfront. The final decision on the acceptability the approach will be dependent on the results that will be reported in the European Public Assessment Report. For time being, there is no experience on the multiple PD marker approach. Therefore, the decision on its approvability is made on case by case.
286-294	8	Comment: We consider that it is important to be clear that it is the study population chosen in efficacy studies will be the most sensitive and should be justified as such. Proposed change: Consider amending the text as follows: 'The study population should be representative of approved therapeutic indication(s) ~~of the reference product~~ and be ~~sensitive~~ justified as being the sensitive for detecting potential differences between the biosimilar and the reference in term of efficacy.'	No. The guideline says that the chosen disease model should be both representative for other therapeutic indications and sensitive for differences. This means that the disease model should cover as many efficacy and safety issues, including immunogenicity, that are relevant for the approved therapeutic indications. To say "most sensitive" would be an oversimplification of the complex situation.
287-289	4	Comment: Please provide clarification if these trials are expected to be Phase I or Phase Ib-type trials? Additionally,	The classification of phases of clinical trials are relevant for the development of new innovative medicines but not for biosimilars. The confirmatory efficacy studies are phase III-like studies. The appropriate statistical power depends on the

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		please clarify what would be considered 'adequate' for such trials – would a power of 80% be sufficient?	study design and the available information concerning the selected efficacy endpoints.
287-289	10	Comment: Referring to "Usually, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference …", we think that "comparative efficacy" is a very high standard if it is a clinical outcome study and is a higher hurdle than the originator product. And if the required design is an equivalence study (Line 296), then this becomes prohibitive and will shut down the biosimilars regulatory pathway. This would potentially result in samples sizes into the thousands, driving sponsors to pursue an original marketing application with a full development program (that would be smaller than a clinical outcomes equivalence program under the biosimilars regulatory pathway). Therefore, the inferiority study design is the prefered option… Thus, it becomes critically important to define what the clinical efficacy endpoint for such equivalence trials should be, which practically speaking should be a biomarker or other relevant PD endpoint. Such endpoints may be more sensitive in detecting clinical differences from the reference product relative to harder clinical outcomes, which often are less common events with greater variability.	The current requirements are very demanding. Nevertheless, they have not prohibited the development of biosimilars for European market. The current GL provides some flexibility for situations where the conduct of full-blown clinical equivalence studies is unreasonable and unnecessary. The use of surrogate markers is described in section 5.2 and study design in section 5.3.1.
287-289	17	**Comment:** The inclusion of comparative efficacy trials should not	The current wording describes the current regulatory thinking and experience based on the existing guidelines and tens of

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		be an automatism but based on clinical reasoning. It may be even counterproductive to repeat the pivotal trial of the reference product. See below. Preferable double-blind is considered rather weak, leaving too much room. If it is decided that a RCT is needed this should provide be unbiased results, By default this is double-blind unless clearly not feasible. **Proposed change:** UsuallyIn certain cases, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in a comparative efficacy trial. E.g. when there is a lack of suitable PD parameters and there is still a need for confirmation of efficacy in a clinical setting. In such a situation it should be considered whether a clinical comparative study would resolve remaining uncertainty on biosimilarity. To this end, efficacy should be compared in adequately powered, randomised, double-blind parallel group comparative clinical trial(s).	scientific advices. However, biosimilarity is an evolving concept. The current draft GL provides flexibility that makes it possible to introduce new, well-justified alternative approaches.
287-289	19	Comment: According to the draft guideline, comparative efficacy studies are expected to be “usually” required. It would be advisable to revise the wording and clearly define cases when efficacy studies may be waived and clinical comparability may be demonstrated based on confirmatory PK/PD studies only. Reference is made	The situations where PD studies may replace clinical efficacy studies with clinical endpoints are discussed in Section 5.2 The scenario of using the “generic approach”, i.e. establishing clinical comparability by pharmacokinetic equivalency is for very simple biologicals.

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		here to lines 218-221 of the draft as well as to the draft of the "*Guideline on Similar Biological Medicinal Products*" (CHMP/437/04 Rev 1). According to this overarching guideline "in specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study may not be necessary if similarity of physicochemical characteristics and biological activity/potency of the biosimilar and the reference product can be convincingly shown and similar efficacy and safety can clearly be deduced from these data and comparative PK data".	
289-291	1	**Comment:** BIO believes that the study population for efficacy trials should be justified as being the most sensitive for detecting any potential differences between the biosimilar and reference biological products. **Proposed change:** "The study population should be representative of approved therapeutic indication(s) of the reference product and **be justified as being the most sensitive for detecting any potential differences between the biosimilar and the reference in terms of safety, efficacy, and immunogenicity."**	No. The guideline says that the chosen disease model should be both representative and sensitive for differences. This means that the disease model should cover efficacy and safety issues, including immunogenicity, that are relevant for the approved therapeutic indications. To say most sensitive would be an oversimplification of the complex situation.
289-291	2	Comment: It is stated that the study population should be representative of approved therapeutic indication(s) of the reference product. However, in a certain situation	No. The current text is more appropriate as general guidance. The use of un-licensed clinical models should be exceptional, well justified and discussed with regulatory authorities upfront.

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		another, probably not yet approved, study population could be more sensitive to test potential differences in terms of efficacy or safety between the biosimilar and the reference products. Therefore, it would be preferable to include in the current draft of the general non-clinical and clinical guideline the wording of the EMA biosimilar mAb guideline(EMA/CHMP/BMWP/403543/2010), i.e.: "Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions (whether licensed or not), and the applicant should justify that the model is relevant as regards efficacy and safety, and sensitive to demonstrate comparability in the indication(s) applied for." Proposed change: The study population should be representative of approved therapeutic indication(s) of the reference product and be sensitive for detecting potential differences between the biosimilar and the reference. Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions (whether licensed or not), and the applicant should justify that the model is relevant as regards efficacy and safety, and sensitive to demonstrate comparability in the indication(s) applied for.	
289-291	8	Comment: This section should emphasize that in general clinical efficacy studies will be required to	No. The proposed changes are unnecessary and redundant.

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		confirm clinical comparability. If the reference product is authorised for more than one clinical indication, the efficacy profile should be studied in the same population as at least one approved therapeutic indication and will have to be justified for each of the claimed indications (with reference to Section 6 for more details). Proposed change: Consider amending the text as follows: '~~Usually~~ In general, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference ….double-blind. ~~The study population should be representative of~~ The biosimilar should be studied in a population in an approved therapeutic indication(s) of the reference product, unless justified and be sensitive for detecting any potential differences between the biosimilar and the reference product. If the reference medicinal product has more than one therapeutic indication, efficacy of the biosimilar has to be justified for each of the claimed indications (see Section 6)**.**'	
289-291	14	Proposed change: The biosimilar should be studied in a ~~study~~ population ~~should be representative of~~ in an approved therapeutic indication(s) of the reference product ~~and be~~ that is justified as being sensitive for detecting any potential differences between the biosimilar and the reference product in term of efficacy, safety and immunogenicity.	No. The proposed changes are unnecessary and redundant.

Immunogenicity: The GL states that the length of the follow up is normally one year for products with chronic administration but can be shorter if justified. The justifications should take into account the characteristics of the product and the experience

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291	8	Comment: We suggest changing Clinical 'praxis' to clinical 'practice'. Proposed change: Consider amending the text as follows: "Occasionally, changes in the clinical ~~praxis~~ practice….."	Agreed.
291	14	Comment: Occasionally, changes in the clinical praxis mandate Proposed change: Editorial: "practice"	Agreed.
291	15	Comment: We propose the following revision Propose change: biosimilar and the reference product taking into consideration the different target populations interested by the approved indications. Occasionally, changes in the clinical practice mandate a deviation…..	The text has been modified.
291	18	Clinical 'praxis' should be changed to clinical 'practice'.	Agreed.
291-294	1	Comment: BIO believes that the clinical comparability study should be conducted in an approved indication for	No. This would be too restrictive. Nevertheless, the use of un-licensed clinical models should be exceptional, well justified and discussed with regulatory authorities upfront.

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		which the reference product (by default) has been studied, because that informs the design, duration and size of the study.	
295	16	The preference for a equivalence trial may have its regulatory logic as the ultimate proof of similarity, but is not in the interest of public health. Patients profit if the product is better and non-inferiority will lower the costs of development. And the if the biosimilar meets all other criteria of biosimilarity the possible difference in efficacy if only non-inferiority is evaluated will be marginal. Manufacturer are now forced to abstain from any improvements in the product because this will be punished by missing the clinical biosimilarity margins.	It is true that the use of the equivalence design sets a very high hurdle. Therefore, the draft GL offers some flexibility for situations where the use of the equivalence design is unnecessary. However, the current concept of biosimilarity does not include “biobetters”.
295-302	1	Comment: BIO believes the clinical study design section should discuss acceptable margins for determining comparability within equivalence or non-inferiority trials. Proposed change: “In general, an equivalence design should be used. The comparability limits for the main outcomes should be defined and justified using scientifically valid, evidence-driven statistical methods prior to conducting the study. The use of a non-inferiority design may be...”	No. The comparability margins are discussed in the next paragraph.
296-299	20	Comment:	If the non-inferiority design will be used, it is expected that

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		("In general, an equivalence design should be used. The use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship."): We agree with the Draft Guideline's note that equivalence designs should be the rule rather than the exception. We urge, however, that the final guideline state that equivalence designs are the most appropriate for biosimilar clinical safety and effectiveness trials. This design is the most suitable for demonstrating biosimilarity because it excludes the possibility of the proposed biosimilar obtaining a "superior" clinical outcome, which would constitute a clinically meaningful difference between the biosimilar and its reference product. Where clinically meaningful differences exist, they may not be uniformly beneficial to patients. Even if they were beneficial, the proposed product would be clinically different, and approval as a biosimilar would not be appropriate. We believe the final guideline should state that the decision that superiority need not be excluded (and that a non-inferiority design may thus be used) should not affect the acceptance criterion for non-inferiority. For example, if a two-sided 95% confidence interval is the standard for comparability testing (allowing 2.5%	the Applicants will follow the ICH guidance on non-inferiority testing (ICH Topic E 9: Statistical Principles for Clinical Trials).

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		error for inferiority and 2.5% error for superiority), a one-sided 97.5% confidence interval should be used for non-inferiority testing to preserve the acceptable error rate. There is no logical, statistical, or scientific reason why the decision not to require a non-*superiority* test should affect the acceptable rate of error for the non-*inferiority* determination.	
296-301	2	Comment: The draft guideline states that the use of a non-inferiority design may be acceptable if justified with a strong scientific rationale and taking into consideration the characteristics of the reference product. This may only be accepted where the possibility of increased efficacy can be excluded on scientific and mechanistic grounds. We highly welcome this possibility for the non-inferiority design. Provided that a biosimilar product has shown to be highly similar to its reference product based on (1) physico-chemical comparability; (2) comparative in vitro binding and functional assay data; and (3) comparability of PK and/or PD data, with the non-inferiority design not only the inferiority can be excluded but it can also be expected that the biosimilar will not be superior to its reference product. Proposed change: A non-inferiority trial may only be accepted where the	Agreed. The superiority testing would require the definition of a clinically meaningful superiority. Thus, the omission of the superiority testing means that clinical superiority can be excluded by scientific and mechanistic grounds.

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		possibility of a significant and clinically relevant increased in efficacy can be excluded on scientific and mechanistic grounds.	
296-301	10	Comment: The draft guideline states that the use of a non-inferiority (NI) design may be acceptable if justified with strong scientific rationale and taking into consideration the characteristics of the reference product. This may only be accepted where the possibility of increased efficacy can be excluded on scientific and mechanistic grounds. We highly welcome this possibility for the NI-design, since a biosimilar product which (1) has shown to be highly similar to its reference product and (2) for which superiority can be addressed by other means, such as mechanistic grounds and appropriate biological testing, like ADCC and CDC testing, is highly unlikely to achieve superior efficacy.	No change proposed.
296-302	15	Comment: We propose to substitute the paragraph as follows Proposed change: The comparability limits for the main outcomes should be defined and justified using scientifically valid, evidence driven statistical methods prior to conducting the study.	No. The comparability margins will be discussed in the next paragraph.

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301	9	Comment: CHMP have required large, comprehensive immunogenicity as a primary variable analysed according to various criteria using a descriptive analysis **Proposed change:** Insert The study of immunogenicity can be sized in patient numbers using a non-inferiority model calculation.	No. Immunogenicity is discussed in the clinical safety chapter. Testing of immunogenicity involves the incidence, titre, neutralising capacity and clinical correlations. Thus, it is difficult to apply simple statistics.
303	16	The main omission in the revision is the discussion of the dose to perform the comparative clinical trial. Apart from immunogenicity and local tolerance all adverse effects of biologics are caused by pharmacodynamic effects. This makes relative potency the most important issue in the comparison between biosimilar and reference. In addition the dose-response curve of biologics is bell shaped. To be able to find differences in clinical efficacy the dose should be in the ascending part of the dose response curve. However, the dose-response of most biologics are not well known and the current doses in the label can be assumed to be at the plateau level of the curve. A comparative phase II like approach is more revealing than a full fledged phase III comparative trial to show equivalence in efficacy and safety. Suggested change: rethink the biosimilarity exercise and formulate new	It is true that most adverse effects of biologicals can be explained by their pharmacological effect. However, the equivalence based on PD marker(s) may not indicate equal safety. It is expected that comparable efficacy and safety is demonstrated by using the approved posology. The use of experimental subtherapeutic doses cannot be recommended for treatment of patients.

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		draft guidelines	
310-312	8	Comment: It would be helpful to be more specific and list the product-class's for which specific guidelines have been prepared and for context to be given so the applicant knows how the guidance fits together as a whole. Proposed change: Consider providing examples of the product-class-specific guideline	No. The hierarchy of the GLs is such that the overarching GL gives the general principles and the product-class-specific will go further into the details. It is expected that the Applicant will read the relevant product-class-specific GL as well.
310-312	18	It would be helpful to be more specific and list them here (for example...) and for context to be given so the applicant knows how the guidance fits together as a whole.	No. The hierarchy of the GLs is such that the overarching GL gives the general principles and the product-class-specific will go further into the details. It is expected that the Applicant will read the relevant product-class-specific GL as well. Scientific advice is recommended for questions that are not answered by the present GLs.
312-313	16	How do I interpret the advice regarding the most sensitive endpoint after reading the EPAR of Grastofil. There the differences seen between biosimilar and reference at low doses were accepted because they were caused by the high sensitivity for differences in potency at that level. So what is the sense of using the most sensitive conditions? Proposed change: delete sensitive and replace with sensible	First of all, the term "most sensitive" is indeed a problematic concept since the "sensitivity" has several dimensions. In addition, the Grastofil case is an example of the problems and solutions when PD studies are used to demonstrate comparable efficacy. Nevertheless, it is still recommended that a sensitive model that can detect clinically meaningful differences and is representative of the relevant therapeutic indications is used to demonstrate clinical comparability.
315-319	10	Comment: The primary endpoints to establish efficacy may be different than that used for initial licensure. This will	No change proposed.

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		require product–by-product justification. We endorse the concept.	
315-321	2	Comment: The draft guideline states that it is not necessary to use the same primary endpoints as those that were used in the marketing authorization application of the reference product. The possibility of using alternative, scientifically justified, i.e. more sensitive primary endpoints for biosimilar comparative studies is appreciated. Therefore, we suggest including the same wording as proposed in this draft version of the non-clinical and clinical biosimilar guideline into the final guideline.	No change proposed.
315-321	17	Comment: This paragraph may be revised. In principle when it is decided a RCT is needed the endpoint that is the most sensitive for showing a difference should be used. As an example in psoriasis usually the proportion of subject clean or almost clean (PASI90 or PASI75) is used as primary endpoint. However the PASI score, as a continuous scale is much more sensitive to show a difference if it exists. Therefore the PASI score has been accepted (in an MRP procedure) and recommended (in scientific advices) as the better outcome endpoint in the context of a biosimilarity exercise.	No. The original text aims to clarify the point that has raised a lot of misunderstandings. The example mentioned in the comment is, unfortunately, not very helpful. The selection of the primary efficacy endpoint requires that there is historical data that can be used to define the clinically significant difference.

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		Proposed change: ~~The correlation between the "hard" clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are sensitive to detect differences may have been demonstrated in clinical trials with the reference product. In this case, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorisation application of the reference product. However, it is advisable to include some common endpoints (e.g. as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product.~~ In the context of therapeutic equivalence exercise it is recommended to use the most sensitive endpoint to show no difference exists. This not is necessarily the primary efficacy endpoints used for the marketing authorisation application of the reference product. However, it is advisable to include these endpoints to facilitate comparisons to the clinical trials conducted with the reference product.	
315-321	20	Comment: ("The correlation between the "hard" clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are sensitive to detect differences may	No. In the comparability studies, the primary efficacy endpoint should be sensitive for differences between the test and the reference. It may not be feasible to use the endpoints that were used in the pivotal trials of the reference product as primary endpoints in the comparability studies. Nevertheless, they may be used for descriptive analysis to control assay

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		have been demonstrated in clinical trials with the reference product. In this case, it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorisation application of the reference product. However, it is advisable to include some common endpoints (e.g. as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product.")): We believe that an applicant should use the endpoints that supported licensure of the reference product, unless different endpoints are scientifically justified. Endpoints that measure other important effects and endpoints that may be more sensitive to detecting potential differences between the two products, however, should also be tested. We suggest that the final guideline note that, when selecting the study population, an applicant should consider whether the population has characteristics consistent with those of the population studied for the reference product, and in particular, whether the patients have different co-morbidities, disease states, or concomitant medications. These factors are important for minimizing confounding patient-specific factors, satisfying the constancy assumption, establishing a margin, and thus evaluating the similarity of clinical results. The final guideline should also note that an applicant	sensitivity. The potential differences between the populations in the pivotal studies of the reference product and the population of the confirmatory efficacy study need also to be considered when assessing the assay sensitivity as pointed out of the draft guideline.

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		should also study the population(s) (and endpoint(s)) sensitive to potential differences between the products. In some cases, the population studied for the licensure of the reference product will not be the population best suited to detecting potential differences between the products. A study in more than one population, or more than one study, may be necessary. In all cases, a biosimilar applicant should justify the populations used during clinical development and indicate in the product labeling which populations were studied.	
316	7	Comment: "Differences" is too broad in this sentence Proposed change: "are sensitive to detect clinical meaningful differences"	Agreed.
322-323	2	Comment: The current draft guideline states that 'Clinical comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product* (see ICH topic E9 Statistical principles for clinical). As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered.' Given that biosimilar clinical trials may use different primary endpoints than the ones used in the pivotal	No. It is appreciated that the current physico-chemical analysis and *in vitro* functional testing may demonstrate a very close similarity between the test and the reference. Nevertheless, more experience and evidence is required to relax the requirement for clinical data. For time being, the CHMP is not willing to accept the asymmetric equivalence margins.

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		trials of the reference product, limited data may be available to justify the margins. Moreover, it should be kept in mind that the clinical trial is the last step in confirming biosimilarity and potentially the least sensitive one to detect differences should any exist. It needs also to be emphasized that the comparability data produced by previously performed physico-chemical, in vitro binding and functional assay studies can provide highly sensitive measures to substantially support the adequacy of the margin selections and similarity. *the reference product could either be the US licensed or EU authorised reference product – according to language as included in the revised draft guideline on biosimilar products (Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev.1) Proposed change: Clinical comparability margins should be pre-specified and justified on both statistical or clinical grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical trials and CHMP guideline CPMP/EWP/2158/99 on the choice of the non-inferiority margin) taking into account that analytical and bioanalytical comparability may be more sensitive by far than clinical trials for evaluating similarity. In cases where an equivalence design is	

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		deemed necessary, asymmetric margins may be considered depending on the level of residual uncertainty and the required need for tightness to control for non-inferiority and for non-superiority. As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered.	
322-323	4	Comment: Should such trials be designed in general using an 80-120% equivalence margin or does it have to justified on a case-by-case basis?	No. The equivalence/non-inferiority margins should be based on the knowledge on the reference product and justified on both statistical and clinical grounds.
322-323	16	If it is allowed to use equivalence margins based on published data for the reference product, why not allow comparison of efficacy data of the biosimilar with historical data, as alternative for a direct comparison in a double blind clinical trial?	The use of historical data to compare the test and the reference is not appropriate because it is impossible to reconstruct the past clinical trials to the degree that reliable comparisons can be made.
322-324	10	Comment: The draft GL states: “Clinical comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical). As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered.” Given that biosimilar clinical trials may use different primary endpoints than the ones used in the pivotal trials of the reference product, limited data may be available to justify the margins. Moreover, it	No. For time being, asymmetrical margins have not been accepted by the CHMP because, from the efficacy point of view, no clinically significant superiority (“biobetter”) is acceptable for a product developed as a biosimilar. Bioanalytical methodology may be more sensitive than clinical testing, but it is not yet proven that all differences that are of clinical significance can be captured.

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		should be kept in mind that the clinical trial is the last step in confirming biosimilarity and potentially the least sensitive one to detect differences should any exist. Proposed change: Clinical comparability margins should be pre-specified and justified on statistical and/or clinical grounds (see ICH topic E9 …) keeping in mind that previously performed analytical and bioanalytical comparability may be far more sensitive than clinical trial data at evaluating similarity. In cases where an equivalence design is deemed necessary, asymmetric margins may be considered depending on the level of residual uncertainty and the required need for tightness to control for non-inferiority and for non-superiority. As for all…	
322-324	14	Comment: The draft GL states: "Clinical comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical). As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered." When defining the comparability margins, the residual uncertainty following the CMC, pre-clinical and PK(/PD) similarity assessments should be taken into account.	No. The current CHMP recommendation is to use the power-based approach to estimate the sample size. It is true that it is sometimes difficult to find the necessary historical data. It is recommend to consulting the regulatory authorities if the Applicant aims to use alternative methods, such as the precision-based estimates.

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		Based on the "totality of evidence" approach, the margins should be selected to rule out meaningful differences and to provide sufficiently precise and robust estimates of the potential difference between the products. In lieu of determining the sample size based on selected comparability margins, methods which are designed around the precision of the estimate, should be considered as a valid alternative when planning the study. Proposed change: "Clinical comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product (see ICH topic E9 Statistical principles for clinical Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev. 1 Page 10/13). In lieu of determining the sample size based on selected comparability margins, methods which are designed around the precision of the estimate, can be a viable alternative when planning the study. As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be considered."	
325	18	It would be worthwhile to state that ethnicity would be expected to have been addressed in the original clinical programme conducted by the originator and therefore	It is true that ethnic factors are rarely important from the biosimilarity point of view. Nevertheless, a justification is needed for the use of data from a population that has a

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		should not be a consideration for a biosimilar.	different ethnic background (see GL CHMP/EWP/692702/08)
327-331	20	Comment: As a general matter, we believe that immunogenicity testing should always be required and recommend that the final guideline make this point clear to biosimilar applicants. A biological product's propensity for producing an immune response may be sensitive to a variety of factors – including its unique manufacturing processes or immediate packaging – and is impossible to predict without clinical testing. As a result, we believe that, even when clinical differences are not anticipated, protecting patient welfare will always require some comparative clinical immunogenicity testing of sufficient duration to assess important differences. ("Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety profile. Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study establishing comparability. Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues related to the reference product."): We suggest that the final guideline explain that it is generally important to compare not only the incidence and severity of an	Partly agreed. Testing for immunogenicity in a comparable manner is generally required as stated in lines 340-344. However, in very specific cases it might not be necessary to perform clinical immunogenicity studies before approval. This will depend on multiple factors including the characteristics of the reference product, information obtained during the biosimilar development, the physicochemical characteristics of the active substance, etc. Agreed. Line 335-338 has been amended as follows: "This includes in particular a description of possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion related reactions and immunogenicity". The comparative immunogenicity studies are further discussed in the 'Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMA/14327/2006). Discussion of interchangeability is outside the scope of the present GL.

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		immune response but also its nature (e.g., cross-reactivity, target epitopes, and neutralizing activity) and consequences (including effects on pharmacokinetics and side effects such as infusion reactions). Similar incidence of immunogenicity between an innovator and proposed biosimilar does not necessarily mean similar immunogenicity. Due to different factors that may cause immunogenicity, two similar complex protein products may be immunogenic in different patients and/or elicit antibodies to different epitopes. Even a proposed biosimilar that exhibits a lower rate of immunogenicity than that of the reference product could produce immune responses that differ significantly in nature (e.g., producing neutralizing antibodies or not) or degree. A less immunogenic proposed biosimilar could therefore have a safety and effectiveness profile that is meaningfully different from that of the reference product. Thus, we believe that the characteristics of the antibody response against a proposed biosimilar should be identified and compared with those of the antibody response against the reference product. The final guideline should provide that the comparison of antibody responses should consider characteristics such as target epitope specificity, neutralizing capacity, titer range, and/or isotype. Differences in these characteristics may result in clinically meaningful differences between the products or imply antigenic	

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		differences that were otherwise undetectable through analytical testing. If a proposed biosimilar elicits antibodies to a specific epitope and the reference product elicits antibodies to another, for example, switching between the products could generate a higher incidence of antibody formation – with potential clinical consequences – than would treatment with either product alone. A proposed biosimilar that elicits antibodies to a different epitope could thus pose concerns even if its immunogenicity is not increased. An applicant should also assess the cross-reactivity of anti-biosimilar antibodies with the reference product. Determining whether antibodies generated to the biosimilar cross-react could inform the biosimilarity determination as well as the labeling of the biosimilar.	
328	3	Comment: The principle of a step-wise development program implies that the goal of a pivotal efficacy study is to evaluate and *confirm* biosimilarity in a specific clinical setting rather than to *establish* comparability. Proposed change: Consider amending the text as follow: Clinical safety is important throughout the clinical development programme and is captured in part during initial PK and/or PD evaluations and ~~also~~ as critical to be evaluated in a sensitive clinical setting with enough	Partly accepted. The sentence has been amended as follows: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and also as part of the clinical efficacy study". The additional information proposed is also captured in lines 330-338.

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		exposure and duration to assess known risks of interest with the reference product and rule out significant unexpected risks with the biosimilar ~~part of the pivotal clinical efficacy study establishing comparability~~.'	
328-329	7	Comment: (…) *is captured during initial PK and/or PD evaluation* (…) Anti-drug antibodies should be included, in addition to PK and/or PD evaluations. Proposed change: (…) is captured during initial PK and/or PD and anti-drug antibody evaluation (…)	Not agreed. Measurement of anti-drug antibodies is part of clinical safety studies and is, thus, captured within the current text.
328-330	1	Comment: BIO believes that the principle of a step-wise development programme implies that the goal of a pivotal efficacy study is to evaluate and *confirm* biosimilarity in a specific clinical setting rather than to *establish* comparability. Proposed change: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and ~~also~~ as part of the	Agreed. The sentence has been amended as follows: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and as part of the pivotal clinical efficacy study".

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		pivotal clinical efficacy study ~~establishing comparability~~."	
328-330	14	Comment: The principle of a step-wise development program implies that the goal of a pivotal efficacy study is to evaluate and *confirm* biosimilarity in a specific clinical setting rather than to *establish* comparability. Proposed change: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and ~~also~~ as part of the pivotal clinical efficacy study establishing biosimilarity ~~comparability~~."	Agreed. The sentence has been amended as follows: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and as part of the pivotal clinical efficacy study".
329	17	Comment: In line with previous comments please adapt Proposed change: ….also as part of ~~the pivotal~~ a clinical efficacy study when performed ~~establishing~~ to confirm ~~comparability~~ biosimilarity	Agreed. The sentence has been amended as follows: "Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and as part of the pivotal clinical efficacy study".
330	19	Comment: According to the draft guideline, data from comparative safety studies should "normally" be collected pre-authorisation. It would be highly advisable to define cases when pre-authorisation	Not accepted. This should be assessed on a case-by-case basis depending on the type and severity of safety issues related to the reference product. This information is captured within product specific guidelines.

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		safety studies could be waived. According to section 5 of the draft (lines 218-221) “in certain cases” confirmatory PK/PD studies may be sufficient to demonstrate clinical comparability (including both efficacy and safety).	
330-331	1	Comment: BIO believes that the safety profile of the reference product is only one piece of information that informs the need for interrogating safety of a biosimilar candidate; in addition, any signals from already-conducted (non-)clinical studies may be informative to the need and scope of safety studies in the pivotal setting. Proposed change: “Comparative safety data should normally be collected pre-authorisation, their amount depending in part on the type and severity of safety issues related to the reference product.”	Not accepted. The known safety profile of the reference product should be the basis for the comparative safety/ efficacy study. Signals obtained during already conducted (non)clinical studies with the biosimilar should always be discussed, especially if new safety signals have arisen.
330-331	8	Comment: The safety profile of the reference product is only one piece of information that informs the need for interrogating safety of a biosimilar candidate; in addition, any signals from already-conducted (non-)clinical studies may be informative to the need and scope of safety studies in the pivotal setting.	Not accepted. The safety profile of the reference product should be the basis for the clinical safety study of the biosimilar. In case new safety signals have been arisen for the biosimilar during previous studies this might question biosimilarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending the text as follows: 'Comparative safety data should normally be collected pre-authorisation, their amount depending in part on the type and severity of safety issues related to the reference product.'	
330-331 and 344	14	Comment: The safety profile of the reference product is only one piece of information that informs the need for investigating safety of a biosimilar candidate (l 330-331), or the amount of immunogenicity data (l 344); in addition, any signals from already-conducted (non-)clinical studies and characteristics of the biosimilar (such as qualitative or quantitative difference(s) of product-related variants, see line 198-201) may be informative to the need and scope of safety studies in the pivotal setting. Proposed change: Line 330-331: "Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues related to the reference product and on signals from previously generated data." Line 344: "The amount of immunogenicity data needed	Not accepted. The main aspects to take into consideration is the experience with the reference product and product class. Reference is made to the Immunogenicity guideline.

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		will depend on the reference product/and or the product class and on the presence (or absence) of qualitative or quantitative difference of product related variants in the biosimilar. “	
335-335	8	Comment: “The applicant should provide in the application dossier an evaluation of the specific risks anticipated for the biosimilar.”It is assumed that this refers to a Risk Management Plan and will follow all the principles defined for the RMP. We propose to state this more explicitly, with a clear reference to Section 7. Proposed change: Consider amending the text as follows: ‘The applicant should provide in the application dossier a Risk Management Plan providing an evaluation of the specific risks anticipated ~~an evaluation of the specific risks anticipated~~ for the biosimilar (see Section 7).’	Partly agreed. This should be discussed in the RMP but also as part of the clinical safety section of the application dossier. The draft guideline has not been amended.
334-335	14	Comment: “The applicant should provide in the application dossier an evaluation of the specific risks anticipated for the biosimilar.”It is assumed that this refers to a Risk Management Plan and will follow all the principles defined for the RMP. We propose to state this more explicitly, with a clear reference to Section 7.	Not accepted. Please refer to previous comment.

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		Proposed change: The applicant should provide in the application dossier ***a Risk Management Plan discussing the limitations of existing data e.g., populations not studied, and identifying safety concerns, which may be an important identified risk, an important potential risk or important missing information*** ~~an evaluation of the specific risks anticipated~~ for the biosimilar (see Section 7)	
339-340	2	Comment: Since the Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use is also referenced, it is recommended to consider revising the wording to incude “therapeutic proteins” and monoclonal antibodies. Proposed change: The principles for the assessment of immunogenicity of therapeutic proteins and monoclonal antibodies have been described in two CHMP guidelines (EMEA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010).	Accepted.
339-344	2	Comment: In the case of certain biological drugs more than one administration route is possible. It is scientifically justified that not all the administration routes exert the	Partly agreed. In case of extrapolation of indication, including another route of administration, this should be carefully discussed within the application dossier. A statement has been included in the extrapolation of indication section of the draft guideline to recommend for a careful evaluation of

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		same immunogenic potential. However, to investigate the similar immunogenic potential of the biosimilar and the reference products, the investigation of the most sensitive administration route is acceptable. Please add the following sentence. Proposed change: If the reference product is authorised for different routes, usually the investigation of the most sensitive route in terms of immunogenicity is appropriate.	different routes of administration and the potential need for additional immunogenicity studies in case this had not been studied as part of the clinical efficacy and safety study.
339-344	19	Comment: With regard to immunogenicity trials, it is frequently hard to define the number of patients needed to be randomised to prove equivalence (or non-inferiority) of the test and reference product based on the incidence of antibody formation. Guidelines cited (EMEA/CHMP/BMWP/14327/2006; EMA/CHMP/BMWP/86289/2010) do not clearly indicate on which basis the number of patients should be defined in immunogenicity trials. It would be of great advantage if the present guideline gave base for sample size calculation in the immunogenicity trials, stating that the number of patients may be calculated based on e.g., selected secondary efficacy parameters.	Not accepted. Testing of immunogenicity involves the incidence, titre, neutralizing capacity and clinical correlations. Providing sample sizes for an immunogenicity study is therefore considered very difficult or impossible.
340-341	7	Comment: "*The potential for immunogenicity of a biosimilar should always be investigated in a comparable*	Partly accepted. Please refer to previous comment.

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		manner" sensitive patient population should be also used. Proposed change: The potential for immunogenicity of a biosimilar should always be investigated in a sensitive population and in a comparable manner (..).	
340-342	8	Comment: We consider that the potential for immunogenicity should always be assessed. Proposed change: Consider amending the text as follows: 'The potential for immunogenicity of a biosimilar should always be investigated in a comparable manner to the reference product and should follow the principles as laid down in the aforementioned CHMP guidelines ~~unless it can be justified that there is a need for deviation from this approach.'~~	Not agreed. In very specific cases it might be able to deviate from the obligatory immunogenicity testing before approval. This will depend on multiple factors including the information obtained during the biosimilar development, the physicochemical characteristics of the active substance, the immunogenicity profile of the reference product etc and should be assessed on a case-by-case basis.
340-342	14	Proposed change: We suggest the following revision: "The potential for immunogenicity of a biosimilar should always be investigated in a comparable manner to the reference product and should follow the principles as laid down in the aforementioned CHMP guidelines ~~unless it can be justified that there is a need for deviation from this~~	Not accepted. In very specific cases it might be able to deviate from the obligatory immunogenicity testing before approval. This will depend on multiple factors including the information obtained during the biosimilar development, the physicochemical characteristics of the active substance, the immunogenicity profile of the reference product etc and should be assessed on a case-by-case basis.

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		~~approach."~~	
340-343	15	Comment: We suggest the following revision Proposed change: The potential for immunogenicity of a biosimilar should always be investigated in a comparable manner to the reference product and should follow the principles as laid down in the aforementioned CHMP guidelines. ~~unless it can be justified that there is a need for deviation from this approach.~~	Not accepted. In very specific cases it might be able to deviate from the obligatory immunogenicity testing before approval. This will depend on multiple factors including the information obtained during the biosimilar development, the physicochemical characteristics of the active substance, the immunogenicity profile of the reference product etc and should be assessed on a case-by-case basis.
345	7	Comment: Two parallel methods should be used, one assay for the biosimilar, and one for the originator molecule based on the same format. In addition, the guideline should specify that all assays should be developed and validated to the best industry standards	Accepted. The sentence has been amended as follows: "Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, which must meet all current standards."
345-346	1	Comment: BIO agrees that the immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, however, it is necessary to be clear that the assays used in all biosimilarity exercises must meet current standards, which may require a new assay to be	Accepted.

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		developed. Proposed change: "Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, which must meet all current standards."	
345-347	15	Comment: We propose to add the sentences in red as follows Proposed change: Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule. If the reference product can be administered both intravenously and subcutaneously, immunogenicity testing should be performed with both routes of administration, especially in case a high risk of immunogenicity is associated to the s.c. administration of the reference product. Assays should be performed with both the reference and biosimilar molecule in parallel ……	Party accepted. Please refer to a previous comment. From a scientific point of view and the step-wise approach there is no valid argument to ask for immunogenicity testing in all accepted routes of administration. This is further discussed in the section on extrapolation.
345-348	14	Comment: The statement that immunogenicity testing of the biosimilar and the reference product should be conducted within the comparability exercise by using	The sentence has been amended as follows: "Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, which must meet

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		the same assay format and sampling schedule is welcomed as this is the prerequisite for a comparison of immunogenicity. However, some further clarification in this regard would be helpful, clearly stating that the same assay format and schedule should be used throughout the comparability exercise. Furthermore, the original tests designed by the innovator may not meet current standards. When assay methods, including sensitivity and specificity) have improved substantially since the approval of the reference compound, past immunogenicity results may no longer be relevant. Also, we suggest to specify that a one assay approach, using one assay that has been qualified against both analytes is the preferred approach for the following reasons: • In order to minimize the potential impact of assay bias on the comparison of immunogenicity of the biosimilar and the reference product, it is preferable to use a single validated assay which is capable to detect antibodies against both the biosimilar and antibodies against the reference product (this has to be demonstrated during assay validation). • When using the two-assay strategy, assay characteristics such as assay cut-points (screening and confirmatory) and assay sensitivity could be	all current standards." Partly accepted. The company developing a biosimilar should decide which approach to use within the biosimilarity excercise. The assay should, at least, identify all patients who produce ADAs and received the potential biosimilar product. This sentence has been added to the guideline. Further guidance on this topic is available in the guideline Guideline on Immunogenicity assessment of therapeutic proteins".

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		different for each assay. This could introduce additional variability that might reduce the reliability of the comparison. It is acknowledged that in some cases the one-assay-approach is not suitable, thus, it should be a case-by-case decision if one or two immunogenicity assays are needed. Proposed change: 'Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule for both products throughout the comparability exercise using an assay which meets all current standards. Assay(s) to detect anti-drug antibodies should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient able to detect antibodies against the biosimilar and the reference product similarly and the suitability of the chosen assay approach has to be demonstrated during assay validation.'	
345-348	20	Comment: ("Immunogenicity testing of the biosimilar and the reference products should be conducted within the	Partly accepted. Please refer to the response to the previous comment.

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		comparability exercise by using the same assay format and sampling schedule. Assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient.")): We suggest that the final guideline clarify that the assay should be optimized for the proposed biosimilar by using the proposed product as reagent. If the assay uses the reference product as reagent, antibodies that react specifically to the proposed biosimilar and not the reference product (i.e., such as in the case where the proposed product differs from the reference product) may be missed. Samples positive for binding to the biosimilar should be tested in an assay for binding to the reference product as well.	
345-349	8	Comment: The statement that immunogenicity testing of the biosimilar and the reference product should be conducted within the comparability exercise by using the same assay format and sampling schedule is welcomed as this is the prerequisite for a comparison of immunogenicity, however some clarity should be provided clearly stating that the same assay format and schedule should be used throughout the comparability exercise it is necessary to be clear that the original tests designed by the innovator may not meet current standards. The assays used in all	The sentence has been amended as follows: "Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule, which must meet all current standards. Regarding the comment related to the assay please refer to the response of the previous comment.

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		biosimilarity exercises must meet current standards, which may require a new assay to be developed., . Furthermore, we suggest that it is not necessary to perform assays with both reference and biosimilar molecules in parallel, and that instead, the assay should be qualified against both analytes, but then run using the biosimilar product for the detection of antibodies as the most conservative approach. The rationale follows • In order to minimize the potential impact of assay bias on the comparison of immunogenicity of the biosimilar and the reference product, it is preferable to use a single validated assay which is capable to detect antibodies against both the biosimilar and antibodies against the reference product (this has to be demonstrated during assay validation). • When using the two-assay strategy, assay characteristics such as assay cut-points (screening and confirmatory) and assay sensitivity could be different for each assay. This could introduce additional variability that might reduce the reliability of the comparison. • When a single assay is used it is recommended to use the biosimilar for detection of antibodies. This is the most conservative approach as all antibodies against the biosimilar will reliably be detected.	

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		It is acknowledged that in some cases the one-assay-approach is not suitable, thus, it should be a case-by-case decision if one or two immunogenicity assays are needed. Therefore we suggest to include a more flexible wording in the guideline. Proposed change: Consider amending the text as follows: 'Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule for both products throughout the comparability exercise using an assay which meets all current standards. Assay(s) to detect anti-drug antibodies should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient and should be able to detect antibodies against the biosimilar and the reference product similarly and the suitability of the chosen assay approach has to be demonstrated during assay validation.	
345-349	10	Comment: The statement that immunogenicity testing of the biosimilar and the reference product should be conducted within the comparability exercise by using	Please refer to the previous comment.

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		the same assay format and sampling schedule is welcomed as this is the prerequisite for a comparison of immunogenicity. However, we suggest to reword the statement in a way that assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient due to the following reasons: • In order to minimize the potential impact of assay bias on the comparison of immunogenicity of the biosimilar and the reference product, it is preferable to use a single validated assay which is capable to detect antibodies against both the biosimilar product and antibodies against the reference product (this has to be demonstrated during assay validation). • When using the two-assay strategy, assay characteristics such as assay cut-points (screening and confirmatory) and assay sensitivity could be different for each assay. This could introduce additional variability that might reduce the reliability of the comparison. • When a single assay is used it is recommended to use the biosimilar for detection of antibodies. This is the most conservative approach as all antibodies against the biosimilar will reliably be detected. It is acknowledged that in some cases the one-assay-	

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		approach is not suitable, thus, it should be a case-by-case decision if one or two immunogenicity assays are needed. Therefore we suggest to include a more flexible wording in the guideline. Proposed change: Assay(s) to detect anti-drug antibodies should be ~~performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient~~ able to detect antibodies against the biosimilar and the reference product similarly and the suitability of the chosen assay approach has to be demonstrated during assay valdidation.	
346-348	16	As in other publications by the CHMP, antigenicity and immunogenicity are apparently considered identical. They are however two different characteristics of a protein. Antigenicity is the capacity of a protein to bind antibodies. It is determined by the epitopes of the protein. If the antigenicity of a biosimilar and the reference can only be different if major structural differences exist. In that case the copy would never qualify as a biosimilar. Immunogenicity is the capacity of a protein to induce antibodies. A precise comparison can only be made in an assay that uses the same antigen. And because biosimilar and reference do not differ in antigenicity by	Please refer to the response to previous comments.

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		definition either of them can be used in the assay. Probably because ideally pre-formulation material is used in the assay and a biosimilar manufacturer only has its own API, the biosimilar is to be preferred in the assay. Proposed change: delete recommendation to test antibodies both to biosimilar as reference.	
346-348	19	Comment: The sentence in lines 346-348 may not be interpretable as concerning analytical blinding only. Proposed changes: <u>Analytical</u> assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient.	Accepted. The draft guideline has been amended as follows "Analytical assays should be performed……..."
346-349	2	Comment: The statement that immunogenicity testing of the biosimilar and the reference product should be conducted within the comparability exercise by using the same assay format and sampling schedule is welcomed as this is the prerequisite for a comparison of immunogenicity. However, we suggest rewording the statement that assays should be performed with both the reference and biosimilar molecule in parallel	Please refer to the response to the previous comments.

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		(in a blinded fashion) to measure the immune response against the product that was received by each patient due to the following reasons: In order to minimize the potential impact of assay bias on the comparison of immunogenicity of the biosimilar and the reference product, it is preferable to use a single validated assay which is capable of detecting both antibodies against the biosimilar and antibodies against the reference product (this has to be demonstrated during assay development and validation). When using the two-assay strategy, assay characteristics such as assay cut-points (screening and confirmatory) and assay sensitivity could be different for each assay. This could introduce additional variability that might reduce the reliability of the comparison. When a single assay is used it is recommended to use the biosimilar for detection of antibodies. This is the most conservative approach as all antibodies against the biosimilar will reliably be detected. In summary, in order to perform comparative immunogenicity testing during biosimilar clinical development, following the demonstration of acceptable bioanalytical comparability and of the capability of the assay to detect antibodies against both the biosimilar and the reference product, immunogenicity assays utilising one set of labelled drug reagent (preferably biosimilar) could be used to detect both the biosimilar and the reference anti-drug antibodies and neutralizing anti-drug antibodies under	

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		the same assay conditions. Blinded measurement of samples is not a concern for this strategy. It is acknowledged that in some cases the one-assay-approach is not suitable, thus, it should be a case-by-case decision if one or two immunogenicity assays are needed. Therefore we suggest including more flexible wording in the guideline. Proposed change: Assay(s) to detect anti-drug antibodies should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient able to detect antibodies against the biosimilar and the reference product similarly and the suitability of the chosen assay approach has to be demonstrated during assay valdidation. It should be ensured that the methods used for anti-drug antibodies and neutralizing anti-drug antibodies detection are able to measure similarly the immune response against the product that was received by each patient, irrespectively of whether the patient was treated with the reference or the biosimilar medicinal product or both.	
346-349	5	Comment: If “the assays should be performed with both the reference and biosimilar molecule in parallel (in a	Partly accepted. In theory, there is a risk for a difference in immunogenicity between the biosimilar and the reference product although biological and physicochemical

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		blinded fashion)", in many cases it is required to repeat the same analysis of one sample using the reference and the biosimilar molecule. Considering the nature of assays being used for the immunogenicity assessments, this will require multiple analyses of immunogenicity samples including ADA screening, ADA confirmatory, Nab screening, Nab confirmatory assessments and the titre determinations. Provided that the physicochemical and biological comparability is demonstrated prior to the clinical studies, it should be accepted to use only one material – either the reference or biosimilar molecule for the immunogenicity assessment if the comparability of the reference and biosimilar molecule in the analysis system is demonstrated during the method validation. By comparing the binding capacity of reference and biosimilar to same positive control, it can be suggested that both drugs are reactive to actual anti-drug antibody of patient in a comparable manner. The approach using one of the drugs (not both drugs) in appropriate validated system enables to avoid unnecessary collecting of excess blood samples from patients. Proposed change: Removal of the requirement or add the condition that "provided that the physicochemical and biological	characterisation has not shown any differences between the two. The assay should at least detect all antibodies to the biosimilar as stated previously.

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		comparability is demonstrated prior to the clinical studies if the comparability between the reference and biosimilar molecule in the analysis system is demonstrated during the method validation, the use of one molecule (either the reference drug or biosimilar) may be justified."	
348-349	2	Comment: It is requested in the current document to measure and present the incidence and titre of developed antibodies, however the relevance of this approach, especially the relevance of titre measurement could be challenged. According to the current scientific thinking it is thought to be irrelevant and the immunogenicity data should be interpreted in light of the "totality of evidence" approach. More specifically differences in detected anti-drug antibody response incidence or magnitude (i.e. titre at screening assay cut-point), even when measured in a directly comparative study using the same bioanalytical method(s), do not provide sufficient evidence of non biosimilarity: the goal is to exclude a negative impact of increased immunogenicity of a biosimilar candidate on clinical parameters. Therefore differences should be assessed in relation to clinical parameters (e.g. altered PK, PD, reduced efficacy, or altered safety profile). Proposed change: Usually the incidence of antibodies and antibody titres	Accepted. The draft guidance has been amended as follows: "Usually the incidence of antibodies and antibody titres should be measured and presented and should be assessed and interpreted in relation to their potential effect on clinical efficacy and safety parameters."

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		should be measured and presented differences in clinically relevant immunogenicity should be assessed and interpreted in relation to their potential effect on clinical efficacy and safety parameters.	
348-349	9	Comment: Experience shows that not only does the CHMP requires us to measure 'the incidence of antibodies and antibody titres' but also to look for evidence of any relationship to SAEs and SARs. Proposed change: Insert "Antibody response, especially neutralising AB, should be analysed against the incidence of serious adverse reactions, and frequency of ADRs."	Partly accepted. Information has been added to the guideline stating that immunogenicity data should be assessed in relation to clinical efficacy and safety.
353-359	2	Comment: It is acknowledged that the duration of immunogenicity data collection during the clinical development of biosimilars should be justified on a case-by-case basis depending on the duration of treatment course and also depending on the level of risk of clinically significant immunogenicity expected based on immunogenicity data obtained with the reference product. Therefore, we suggest including the same wording in the final guideline as proposed in this draft version of the non-clinical and clinical biosimilar guideline.	Accepted.

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353-359	8	Comment: The presence of anti-drug antibody response should be tested in all patients recruited into clinical trials and for the duration of the treatment that supports approval. This information will provide the overall incidence of immunogenicity which should be included in the product label. In addition, we consider that the profile of the reference product in combination with data generated for the biosimilar should inform the assessment for immunogenicity. The investigation of the immunogenicity profile should be driven by the need to ensure there are no unexpected immunogenicity issues with the product under investigation. Therefore, we would like to suggest that in the case of chronic administration the assessment of immunogenicity for the biosimilar including the length of the follow-up data pre-licensing should be based on the immunogenicity profile of the reference product, with the potential need to provide data for an additional period, up to one year, as a post authorisation commitment. Additionally, the agency should clarity whether the described approach is applicable to all classes of biosimilars (i.e. including monoclonal antibodies) or if this is intended to apply to inherently less immunogenic smaller biotech proteins. Proposed change:	Not accepted. Current thinking within the biosimilar development supports the need for one year immunogenicity data pre-licensing for products intended for chronic use. In several cases a shorter follow-up is accepted based on the experience with the reference product, which should be assessed on a case by case basis. This guideline, including the section on immunogenicity, is applicable to the development of all biosimilars, including monoclonal antibodies.

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		Consider amending the text as follow: 'Duration of follow-up should be justified based on the time course and characteristics of unwanted immune responses described for the reference medicinal product, and the characteristics of the biosimilar ~~e.g. a low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity over time.~~ In case of chronic administration, ~~one year~~ follow up data ~~will normally be required pre-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified~~ should be generated for the duration of the clinical trial treatment which support approval and be based on the totality of the available information e.g. the immunogenicity profile of the biosimilar, scientific knowledge and experience of the reference product etc. Further immunogenicity data for ~~the~~ an additional period, up to one-year, could then be submitted post-authorisation.'	
353-359	10	Comment: We consider the profile of the reference product as the guiding principle also for assessing immunogenicity, therefore we would like to suggest that in the case of chronic administration the assessment of immunogenicity for the biosimilar including the length of the follow-up data pre-licensing should be based on the immunogenicity profile of the reference product. With the potential need to provide data for an additional period, up to one year, as post-authorisation	Please refer to the previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		commitment. Proposed change: Line 356: In case of chronic administration, ~~one-year~~ follow up data ~~will normally be required pre-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified~~ should be generated for the duration of the clinical trial treatment which support approval and be based on the immunogenicity profile, scientific knowledge and experience of the reference product. Further immunogenicity data for ~~the~~ an additional period, up to one-year, could then be submitted post-authorisation. In addition, switching data may provide more real-world experience on immunogenicity that would justify less than one-year exposure data wherein under chronic administration switching from the originator to the biosimilar is anticipated."	
353-359	14	Comment: The presence of anti-drug antibody response should be tested in all patients recruited into clinical trials and for the duration of the treatment that supports approval. This information will provide the overall incidence of immunogenicity which is included in the product label. In addition, we consider the profile of the reference product in combination with data generated for the biosimilar should inform the assessment of immunogenicity. The investigation of the immunogenicity profile should be driven by the need to	Please refer to the previous comment.

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		ensure there are no unexpected immunogenicity issues with the product under investigation. Therefore we would like to suggest that in the case of chronic administration the assessment of immunogenicity for the biosimilar including the length of the follow-up data pre-licensing should be based on the immunogenicity profile of the reference product. With the potential need to provide data for an additional period, up to one year, as post-authorisation commitment. The agency should also clarify whether the described approach is applicable to all classes of biosimilars (i.e. including monoclonal antibodies) or if this is intended to apply to inherently less immunogenic smaller biotech proteins. Proposed change: Line 356: "Duration of follow-up should be justified based on the time course and characteristics of unwanted immune responses described for the reference medicinal product, and the characteristics of the biosimilar ~~e.g. a low risk of clinically significant immunogenicity or no significant trend for increased immunogenicity over time.~~ In case of chronic administration, ~~one year~~ follow up data ~~will normally be required pre-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified~~ should be generated for the duration of the clinical trial treatment	

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		which support approval and be based on the totality of the available information e.g. immunogenicity profile, scientific knowledge and experience of the reference product. Further immunogenicity data for ~~the~~ an additional period, up to one-year, could then be submitted post-authorisation."	
356-359	2	Comment: During the immunogenicity assessment of a biosimilar the guiding principle should be the reference product profile, therefore in the case of chronic administration, the assessment of immunogenicity for the biosimilar including the length of the follow-up data pre-licensing should be based on the immunogenicity profile of the reference product. The potential need to provide data for an additional period, up to one year, as a post-authrisation commitment should be evaluated. Proposed change: In the case of chronic administration, one-year follow up data will normally be required pre-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified should be based on the immunogenicity profile, scientific knowledge and experience of the reference product. Further immunogenicity data for the an additional period, up to one-year, could then be submitted post-authorisation. In addition, switching data may provide more real-world experience on immunogenicity that would justify less than one-year	Not accepted. Information on switching is valuable for use in clinical practice. However, the principle of biosimilarity is to show comparability in all aspects described in this guideline, including immunogenicity. Data on switching will not replace data on relative immunogenicity from head-to-head comparisons.

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		exposure data during which under chronic administration switching from the originator to the biosimilar is anticipated.	
356-359	20	Comment: ("In case of chronic administration, one-year follow up data will normally be required pre-licensing. Shorter follow-up data pre-licensing (e.g. 6 months) might be justified based on the immunogenicity profile of the reference product. Immunogenicity data for the additional period, up to one-year, could then be submitted post-authorisation."): We agree with this position.	Accepted.
357-359	1	Comment: BIO believes that specific definition of the features of the immunogenicity profile of the reference product (*e.g.*, immunogenicity rate, clinical consequences of immunogenicity, *etc*.) that would justify shorter follow-up data pre-licensing for chronically administered products would benefit the draft guideline.	Not accepted. This should be based on a case-by-case basis and is based on scientific knowledge and experience. Product specific guidance on the duration of immunogenicity studies is described in the product specific guidance.
35-359	18	The agency should clarify in principle whether this could be applicable to all classes of biosimilars (i.e even monoclonal antibodies) or if this is intended to apply to inherently less immunogenic smaller biotech proteins or whether it would depend on the safety/immunogenicity of the reference product. Currently this context is lacking. At the EMA workshop held on 31st October 2013 it was stated that shorter	Accepted. The draft guidance has been amended as proposed.

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		follow up pre-licensing (e.g. 6 months) might be justified depending on the safety/immunogenicity profile of the reference product e.g. in the biosimilar epoetin guidance it is stated that 12 months comparative immunogenicity is required pre-licensing and this is due to the fact that it takes longer for antibodies to be developed against this class of product compared to insulins for example, where the biosimilar insulin guidance states that 6 months comparative immunogenicity data is required pre-licensing. Providing reference to product specific biosimilar guidance would be helpful. Proposed text: 'Shorter follow-up data pre-licensing (e.g. 6 months) might be justified based on the immunogenicity profile of the reference product. Immunogenicity data for the additional period, up to one year, could then be submitted post-authorisation. For specific examples refer to product specific biosimilar guidance.	
360-361	2	Comment: It is stated in the draft guideline that higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. Although it is acknowledged that in such cases in depth analysis of available immunogenicity data should be required, it is recommended to follow the totality of evidence	Partly accepted. The guideline states that increased immunogenicity will question biosimilarity. In such a situation, clarification is needed.

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		approach here as well. Namely, higher immunogenicity would not necessarily preclude approval as a biosimilar in case it can be justified that the observed higher immunogenicity has no clinically meaningful impact either on efficacy or safety measures. Furthermore, the meaning of the term 'higher immunogenicity' is not defined anywhere (e.g. higher in several timeponts, higher number of positive samples, or higher titres and the limits). Without clinically meaningful impact on efficacy and safety setting the margins for higher immunogenicity is deemed to be questionable. According to the current scientific thinking it is thought to be irrelevant and the immunogenicity data should be interpreted in light of the "totality of evidence" approach. More specifically differences in detected anti-drug antibody response incidence or magnitude (i.e. titre at screening assay cut-point), even when measured in a directly comparative study using the same bioanalytical method(s), do not provide sufficient evidence of non-biosimilarity: the goal is to exclude a negative impact of increased immunogenicity of a biosimilar candidate on clinical parameters. Therefore differences should be assessed in relation to clinical parameters (e.g. altered PK, reduced efficacy, or altered safety profile). Also see the comment on lines 348-349. Proposed change: A higher immunogenicity as compared to the reference	

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		product may become an issue for the benefit/risk analysis and would question biosimilarity. In case higher immunogenicity is detected, the clinical relevance should be evaluated together with the neutralizing potential of the anti-drug antibodies with special emphasis on the assessment of clinically meaningful impact on efficacy and safety.	
360-361	10	Comment: It is stated in the draft guideline that higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. Although it is acknowledged that in such cases in depth analysis of available immunogenicity data should be required, it is recommended to follow the totality of evidence approach here as well. Namely, higher immunogenicity would not necessarily preclude approval as a biosimilar in case it can be justified that the observed higher immunogenicity has no clinically meaningful impact neither on efficacy nor safety measures. Furthermore, the meaning of the term 'higher immunogenicity' is not defined anywhere (e.g. higher in several timeponts, higher number of positive samples, or higher titres and the limits). Without clinically meaningful impact on efficacy and safety setting the margins for higher immunogenicity is deemed to be questionable. According to the current scientific thinking it is though to be irrelevant and the immunogenicity data should	Partly accepted.

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		be interpreted in light of the "totality of evidence" approach. More specifically differences in detected anti-drug antibody response incidence or magnitude (i.e. titre at screening assay cut-point), even when measured in a directly comparative study using the same bioanalytical method(s), do not provide sufficient evidence of non-biosimilarity: The goal is to exclude a negative impact of increased immunogenicity of a biosimilar candidate on clinical parameters. Therefore differences should be assessed in relation to clinical parameters (e.g. altered PK, reduced efficacy, or higher incidence of infusion reactions). Also see the comment on lines 348-349. Proposed change: A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. In case higher immunogenicity is detected the clinical relevance should be evaluated together with the neutralizing potential of the anti-drug antibodies with special emphasis on the assessment of clinically meaningful impact on efficacy and safety.	
360-368	17	Comment: *In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the*	Partly accepted.

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		reference product. This is incorrect. Indeed the biosimilar is more efficacious but not because a better intrinsic PD but because of evoking fewer antibodies. Proposed change: A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the biosimilar is also possible scenario, which would not preclude approval as a biosimilar. In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could ~~erroneously suggest~~ indicate that the biosimilar is more efficacious than the reference product. A ~~It is therefore recommended to pre-specify an additional exploratory~~ subgroup analysis ~~of efficacy and safety~~ in those patients that did not ~~mount an anti-drug antibody response during the clinical trial.~~ develop antibodies is warranted. This subgroup analysis could be helpful to establish that the intrinsic efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response.	
360-370	8	**Comment:** We understand why increased immunogenicity raises questions about biosimilarity, since this could potentially impact both safety and efficacy. However it	Partly accepted. A higher immunogenicity for the biosimilar is will question biosmilarity. Lines 360-368 have been amended as follows: "Increased immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, also a lower immunogenicity for the biosimilar is a possible scenario,

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		is not clear why decreased immunogenicity does not necessarily raise the same level of concern about biosimilarity when considering approval. The draft guideline points out the impact on efficacy of decreased immunogencity, but does not discuss the impact on safety. We believe that the impact on safety should also be discussed, in particular the potential risk of over-dosing patients. It should also be noted that not only neutralising antibodies can have an effect on the efficacy of the drug but also binding and clearing antibodies. In addition, a decrease in immunogenicity could be the result of a difference between the products that is not reflected in an abbreviated development program. The sponsor should be required to justify why additional testing is not needed to further explore this potential difference. Finally, data from many approved biologicals, indicate that immunogenicity differs from indication to indication. It is more appropriate to assume the default that that will likely differ rather than to infer that they could. In any case, absence of immunogenicity assessment in certain indications needs to be justified, and should not be optional. **Proposed change:** Consider amending the text as follows:	which would not preclude approval as a biosimilar. In case of reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This subgroup analysis could be helpful to establish that the efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response. Lines 369-370 have been removed from this section of the guideline. Reference is made to the section on Extrapolation.

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		'A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the biosimilar is also possible scenario. ~~which~~ In both instances the impact on efficacy and safety should be thoroughly discussed although either would not necessarily a priori preclude approval as a biosimilar. Further investigation into the cause of lower immunogenicity is warranted in order to provide a scientific explanation for the observed differences and in order to exclude other clinically meaningful differences. In case of reduced development of neutralizing and/or clearing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This subgroup analysis could be helpful to establish that the efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response. For biologicals with multiple indications, immunogenicity ~~could~~ is likely to differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar ~~may have~~ will need to be justified'	

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361-368	1	Comment: BIO believes that the impact of decreased immunogenicity on safety should also be discussed, in particular the potential risk of over-dosing patients. Also, because lower immunogenicity may act as a sensitive biomarker to signal a potential difference between the biosimilar and the reference product, BIO recommends including a statement that further investigation into the cause of lower immunogenicity is warranted in order to exclude other clinically meaningful differences. Proposed change: "A higher immunogenicity as compared to the reference product may become an issue for the benefit/risk analysis and would question biosimilarity. However, a lower immunogenicity for the biosimilar is also possible scenario and for this case the impact on efficacy and safety should be discussed; depending upon the impact on efficacy and safety, lower immunogenicity~~, which would not~~ may preclude approval as a biosimilar. In case of reduced development of neutralizing and/or clearing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product."	Accepted. Please refer to the text shown above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
361-368	14	Comment: Lower immunogenicity may act as a sensitive biomarker to signal a potential difference between the biosimilar and the reference product. Furthermore, not only neutralizing antibodies can have an effect on the efficacy of the drug but also binding and clearing antibodies, which could be mentioned. Finally, data from many approved biologicals, as included in their labels, indicate that immunogenicity differs for the majority of them when used and approved in multiple indications. It is more appropriate to assume the default that that will likely differ rather than to infer that they could. In any case, absence of immunogenicity assessment in certain indications needs to be justified, this is not optional. Proposed change: However, a lower immunogenicity for the biosimilar is also a possible scenario, which would not a priori preclude approval as a biosimilar. In both scenarios, the impact on efficacy and safety should be thoroughly discussed and further investigation into the cause(s) of different immunogenicity is warranted in order to provide a scientific explanation for the observed differences and to exclude other clinically meaningful differences, in particular because immunogenicity differs	Please refer to the proposed text shown previously.

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		from indication to indication. "In case of reduced development of neutralizing and/or clearing antibodies with the biosimilar, …immune response" For biologicals with multiple indications, immunogenicity ~~could~~ is likely to differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar ~~may have~~ has to be justified	
362-365	2	Comment: In the draft guideline it is stated that reduced development of neutralizing antibodies with the biosimilar can lead to an erroneous analysis of the entire study population which could suggest that the biosimilar is more efficacious than the reference product. It needs to be pointed out that not only neutralizing antibodies can have an effect on the efficacy of the drug but also binding and clearing anti-drug antibodies. Therefore it is also suggested to mention that clearing antibodies can also lead to reduced efficacy. Proposed change: In case of reduced development of neutralizing and/or binding and clearing anti-drug antibodies with the biosimilar, the efficacy analysis of the entire study	Please refer to the amended section shown previously.

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		population could erroneously suggest that the biosimilar is more efficacious than the reference product.	
362-365	10	Comment: The draft guideline says that reduced development of neutralizing antibodies with the biosimilar can lead to an erroneous analysis of the entire study population, which could suggest that the biosimilar is more efficacious than the reference product. We would like to point out that not only neutralizing antibodies can have an effect on the efficacy of the drug but also binding and clearing antibodies. Therefore we suggest to also mention that clearing antibodies can also lead to reduced efficacy. Proposed change: "In case of reduced development of neutralizing and/or clearing antibodies with the biosimilar, …"	Please refer to the amended section shown previously.
363-368	16	This is a remarkable position. Apparently there are real non-responders and non-responders because of immunogenicity. However it cannot be excluded that there are non-responders because of an immunogenic response not leading to a detectable level of circulating antibodies and we do not know of any product at exactly what level of antibodies the efficacy is inhibited.	Not accepted. It is acknowledged that there might be non-responders due to an immunogenic response not leading to a detectable level of circulating antibodies. The proposed subgroup analysis is meant to help characterising the efficacy of a biosimilar independently of its immunogenicity, i.e. identify a seemingly higher efficacy in the ITT population. Since in the mentioned scenario the anti-drug antibodies can by definition not be detected, these patients will then be included in the subgroup of patients without an immune

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		Proposed change: delete this paragraph	response. This may indeed influence the result, but it could be anticipated that there may not be many patients where this is the case. In any case, since these anti-drug antibodies are not detectable, there is no alternative, and BMWP/CHMP considers the proposed subgroup analysis helpful and necessary.
369-370	1	Comment: Data from the labels of many approved biological products indicate that immunogenicity differs when used and approved in multiple indications. BIO believes, therefore, that it is more appropriate to assume the default that immunogenicity will likely differ among indications. Proposed change: "For biologicals with multiple indications, immunogenicity ~~could~~ is likely to differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar ~~may have~~ will need to be justified."	Please refer to the amended section shown previously.
369-370	2	Comment: It is stated in the guideline that for biologicals with multiple indications, immunogenicity could differ among indications and an absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified. It is requested by the guideline that comparative immunogenicity should be	Not accepted. Immunogenicity is dependent of multiple factors, including the product, the route of administration, the patient, concomitant medication, the indication etc. and should therefore be assessed on a case-by-case basis taking these factors into account.

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		evaluated in the most sensitive patient population where the immune reponse of the patients is the least affected. Proposed change: For biologicals with multiple indications, immunogenicity could differ among indications and an absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified only if data were not gained from the most sensitive indication for immunogenicity assessment purposes.	
369-370	10	Comment: The statement that "for biologicals with multiple indications, immunogenicity could differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified" is only applicable if respective data from the reference product are available. Thus, we suggest to modify this sentence. Proposed change: "For biologicals with multiple indications, immunogenicity could differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified in case clinical experience and available data from the reference product exist.	Not accepted. Absence of immunogenicity data in a specific indication has to be justified.

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369-370	20	Comment: ("For biologicals with multiple indications, immunogenicity could differ among indications and absence of immunogenicity assessment in a particular indication for the biosimilar may have to be justified."): As we discuss in greater detail below, the extrapolation of clinical data from one indication to another is often risky and inappropriate, even in cases where mechanisms of action are believed to be the same. These dangers highlight the need for robust pharmacovigilance after a biosimilar receives marketing authorisation. We support the inclusion of a new discussion of extrapolation in the Draft Guideline. This issue warrants great caution, because differences between two biological products that are otherwise highly similar may not manifest in a first indication but will then reveal themselves clinically in a second indication. Indeed, this has been observed recently in Europe. The European Commission approved a biosimilar erythropoietin product (sold under the names Binocrit, epoetin alfa Hexal, and Abseamed) for intravenous administration for patients with chronic renal failure. When the product was later tested in the same patient population for subcutaneous administration, two patients developed neutralizing anti-EPO antibodies (pure red cell aplasia (PRCA) was confirmed in one patient), and the clinical trial was stopped. There are	The extrapolation of indication section of the draft guideline has been amended as stated previously.

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		other examples of biologics with critical aspects that manifest differently in different settings depending on various factors – for example, which molecular activities are needed for safety and efficacy, to which tissues the molecule must penetrate, the dose and route of administration, and the target population's susceptibility to potential drug effects. For this reason, extrapolation of safety and efficacy of a biosimilar to a new indication or clinical setting following highly limited or no clinical testing can carry significant risks to patients.	
371-372	16	Extrapolation is one of the major issues in the biosimilar pathway. Without extrapolation no abridged procedure and without abridged procedure there is no reason for a biosimilar regulatory pathway. Therefore the criteria for justification of extrapolation should be discussed in more depth. Distinction should be made for the type of extrapolation: efficacy, safety and/or immunogenicity. Criteria for the justification of both the reference indication as well as the extrapolated indication should be discussed in detail. **Proposed change:** rewrite and expand the section concerning extrapolation.	The chapter has been revised. Detailed guidance on the extrapolation is difficult as it is based on the "totality of evidence" i.e. all single observations are evaluated against the background of all data gathered during the extensive comparability exercise. Biosimilarity is an evolving concept which is dependent on the progression of scientific knowledge, methodology and experience. Therefore, the guidance should offer flexibility to accommodate novel approaches. A detailed recipe as how to extrapolate in different situations is not possible in an overarching GL. The current text gives the principles of criteria that need to be considered in the justification of the extrapolation and in the planning of additional studies to support extrapolation.
371-388	2	Comment: We appreciate the possibility that indications may be extrapolated in case appropriate justification is	This GL deals with (non)clinical issues. Thus, the concept of biosimilarity is explained in the GL on similar biological medicinal products (CHMP/437/04 Rev. 1).

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		provided. We agree that the extrapolation of indication should be based on the totality of the data. While we agree that the mechanism of action needs to be taken into account, we believe the following factors play equally or even more important roles: • The demonstration of a high level of structural (as demonstrated by physico-chemicalcharacterization) and functional (as demonstrated by in vitro biological assays) similarity. • The demonstration of similarity regarding pharmacokinetics in humans. • The demonstration of similar efficacy and safety in a single, most sensitive indication. More specifically, the population in which differences in safety, especially immunogenicity, and efficacy are most likely to be detected should be chosen for the study. Immunocompetence of the specific patient population and large effect size will be the key criteria for the selected indication which would also support practical considerations, such as the feasibility of the clinical development. The guideline should acknowledge that physico-chemical characterization and non-clinical studies, especially in vitro bioassays for the purpose of	The chapter 6 on extrapolation has been revised. It is agreed in that the extrapolation is based on the totality of evidence rather than on a set of individual tests to solve all issues related to biosimilarity separately. In principle, the absence of any clinically relevant differences regarding structural components and functionalities will allow extrapolation. However, the definition of a particular difference as clinically relevant or irrelevant is not always possible without additional (non)clinical studies. **The mechanism of action of the reference product is important with regard to its active sites.** It is expected that the Applicant is able to justify the extrapolation by providing evidence for a comparable activity of the binding sites. It is believed that the current text is sufficient considering the state on the current knowledge and experience.

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		biological characterization, are the most sensitive tools for detecting differences and for demonstrating a high level of similarity. We also believe that the relevance of the mechanism of action is overstated in the guideline, as it implies that extrapolation is only possible to patient populations in which the mechanism of action is the same as in the studied patient population. We do not believe this is so important for the following reasons: I. A biosimilar is systematically developed to match the originator product in all of its physico-chemical and functional (as tested in biological studies) characteristics and in its pharmacokinetic behavior. This being the case, science dictates that both the biosimilar and reference products will also act in the same way in different patient populations. II. The principle of mechanism of action for extrapolation does not necessarily correlate with the sensitivity of a patient population to detect potential differences. Studying the drug in a patient population with the least affected immune system and with a large effect size will provide much better reassurance for extrapolation. Since the originator product was shown to be effective in all its authorised indications,	

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		and the similar clinical efficacy and safety of the proposed biosimilar product is demonstrated in the most sensitive patient population, no reason could be identified which could question the applicability of the principle of extrapolation. III. The mechanism of action is not always fully understood in different disease conditions and several functionalities of the molecule may contribute to it. In conclusion, the mechanism of action alone is not a well established parameter for determining the possibility of extrapolation. Proposed change: In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. Justification will depend on, e.g., the product's structural and functional similarity to the reference product (including in vitro non-clinical data on relevant functionalities), the product's pharmacokinetic similarity to the reference product, the selection of a patient population for the efficacy and safety study that is sensitive in detecting potential clinically relevant differences taking into account the mechanism (s), the clinical experience and the available literature data. In the absence of any	

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

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371-388	10	**Comment:** We appreciate the possibility that indications may be extrapolated provided appropriate justification is provided. We agree that the extrapolation of indication should be based on the totality of the data. While we agree that the mechanism of action needs to be taken into account, we believe the following factors play equally or even more important roles: • The demonstration of a high level of structural (as demonstrated by analytical characterization) and functional (as demonstrated by biological assays) similarity. • The demonstration of similarity regarding pharmacokinetics. • The confirmation of similar efficacy and safety in a single human study. The population for this study should be chosen in a risk-based manner regarding the patient population, i.e. the population in which differences in safety, especially immunogenicity, and efficacy are most likely to be detected ("most sensitive patient population"). Immunocompetence and large effect size will be the key selection criteria. Practical considerations (feasibility) must also be taken into consideration.	This GL deals with (non)clinical issues. Thus, the concept of biosimilarity is explained in the GL on similar biological medicinal products (CHMP/437/04 Rev. 1). The chapter 6 on extrapolation has been revised. It is agreed in that the extrapolation is based on the totality of evidence rather than on a set of individual tests to solve all issues related to biosimilarity separately. The mechanism of action of the reference product is important with regard to its active sites. It is expected that the Applicant is able to justify the extrapolation by providing evidence for a comparable activity of the known active sites. The concept of "most sensitive population" may not be realistic because of incomplete data on the relative sensitivity of the possible models in efficacy, safety and immunogenicity. Nevertheless, it is expected that the chosen clinical model is sensitive for differences in safety, efficacy, and immunogenicity. It is believed that the current text is sufficient considering the state on the current knowledge and experience.

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		We therefore suggest to strengthen these elements in the guideline. **Proposed change:** In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. Justification will depend on, e.g., **the product's structural and functional similarity to the reference product (including *in vitro* non-clinical data on relevant functionalities), the product's pharmacokinetic similarity to the reference product, the selection of a patient population for the efficacy and safety study that is sensitive in detecting potential differences, the** clinical experience **and the** available literature data. ~~ms of action of the active substance of the reference product in each indication (including its degree of certainty), and on receptors involved. Binding of the reference substance to the same receptors may have different effects in different target cells depending on differences in the intracellular signalling pathways, e.g. due to transformation. This situation is not an argument for additional studies. However, if there is evidence that different active sites of the reference product or different receptors of the target cells are involved in different therapeutic indications or that the safety profile of the product differs between the~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~therapeutic indications, additional data may be needed to justify the extrapolation of safety and efficacy from the indication studied in the pivotal clinical trial.~~ For the extrapolation of safety, the Applicant should consider patient-related factors, such as different co-medication, co-morbidities, and immunological status, and disease-related factors, such as reactions related to the target cells, e.g. lysis of tumour cells. The extent of such data should be considered in the light of the totality of evidence derived from the biosimilar comparability exercise and the potential remaining uncertainties.	
371-388	17	Comment: It is unclear when additional studies would be needed and when not, and if so what kind of studies. A biosimilar should be highly similar and have similar biological/functional characteristics as the reference product relevant for the accepted indications. This should be the basis for accepting all of the indications. Confirmation of similar efficacy should not rely on confirmatory efficacy trials in other indications than those evaluated thus far for the biosimilar. Rather this should be inferred from high similarity demonstrated in a comparability exercise encompassing physico-chemical and biological characterisation, in vitro functional activity and similar PK and PD data. In line with the principle that a biosimilar is highly similar to its reference product, and provided this is	The chapter 6 on extrapolation has been revised. We agree that, ideally, demonstration of similar biological/functional characteristics of the test and the reference would be sufficient to conclude biosimilarity in all therapeutic indications without confirmatory clinical trials. The GL states that once comparability has been demonstrated in one therapeutic indication, extrapolation is the expectation. The guidelines for biosimilars are based on the legislation (Directive 2001/83/EC) where it is stated that “Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines”.

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		adequately confirmed, the extrapolation should be presumed to be possible. This is a straightforward conclusion based on the principle of high similarity. If there are data which indicate that extrapolation of indications is not possible, then (by implication) this is due to a 'significant' difference between biosimilar and reference product. The presence of such a 'significant' difference is never acceptable, both as a matter of principle, and for the practical reason that switching between biosimilar and reference product may occur in clinical practice. There may be cases where uncertainty remains with respect to the possibility to extrapolate to other indications. This may call for additional data and the Applicant should justify the adequacy of the data package. Besides efficacy, pharmacokinetics or safety may be different in different patient populations. This does not contradict biosimilarity nor is it expected that this would call for additional data. However, it should be considered that for some products a study in one patient population may be most sensitive regarding efficacy, whereas another patient population may be more sensitive with respect to immunogenic potential. Proposed change: "~~In case the reference medicinal product has more~~	The comment implies that PK and PD data should be sufficient to complement the physic-chemical and functional in vitro data. This may be the case but there are not yet sufficient data or experience to draw this conclusion. The concept of the "most sensitive" clinical model is not realistic as mentioned in the comment. Nevertheless, assessing efficacy, safety and immunogenicity in one model/therapeutic indication has several advantages and is sufficient provided that it is sensitive for differences. For time being, the current text is regarded appropriate.

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

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		~~uncertainties~~ *In principle, in case biosimilarity is shown, extrapolation between indications would be acceptable. However, if data indicate differences in biological functionality, even when this would affect some indications only, this would contradict the concept of biosimilarity since comparable activity for the whole spectrum of biological functions is required. In that case the product could not be accepted as a biosimilar; a stand alone application might be more appropriate.* *In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data may be needed. The Applicant should justify the extent and adequacy of the data package provided.* *It should be considered, that due to patient-related factors the sensitivity of a trial to detect differences in efficacy or in immunogenic potential may differ between patient populations."*	
373-375	7	Comment: It should be again specified that immunogenicity should be tested in the most sensitive population. Proposed change: In case the reference medicinal product has more than	No. There are usually no reliable comparative data on the level of immunogenicity of a particular product in different therapeutic indications. In addition, testing immunogenicity in one therapeutic indication and efficacy and safety in another therapeutic indication makes no sense. Nevertheless, the chosen therapeutic indication should be sensitive for differences.

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		one therapeutic indication, the efficacy and safety (including immunogenicity in the most sensitive patient population) of the biosimilar has to be justified (…)	
373-375	8	Comment: This section should be re-worded as it seems inconsistent with current thinking i.e the level of evidence of biosimilarity (Quality, non clinical , PK) should be taken into account in determining if any additional clinical studies are needed beyond the clinical comparative study in the most sensitive population. It will be more difficult to extrapolate between diverse indications where separate studies may be needed. The current wording highlighted is mis-leading. If the applicant had to perform a clinical study in each of the indications it would likely be because the product was not shown to be biosimilar at the earlier stages and therefore couldn't be developed as a biosimilar. Proposed change: Consider amending the text as follows: 'In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified ~~or, if necessary, demonstrated separately~~ for each of the claimed indications. This justification may include clinical	The wording has been modified in order to avoid misunderstandings.

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		efficacy and safety data.	
373-375	18	This section should be re-worded as it seems inconsistent with current thinking i.e the level of evidence of biosimilarity (Quality, non clinical , PK) should be taken into account in determining if any additional clinical studies are needed beyond the clinical comparative study in the most sensitive population. It will be more difficult to extrapolate between diverse indications where separate studies may be needed. The current wording highlighted is mis-leading. If the applicant had to perform a clinical study in each of the indications it would likely be because the product was not shown to be biosimilar at the earlier stages and therefore couldn't be developed as a biosimilar. Proposed text: Delete the following text in the current guidance (line 374): 'or, if necessary, demonstrated separately for each of the claimed indications' Replace the above text with the following (adapted from MAbs guidance): 'Extrapolation of clinical efficacy and safety data to other indications of the reference biotech protein, not specifically studied during the clinical development of the biotech protein, is possible based on the results of	The wording has been modified in order to avoid misunderstandings. The text in the Annex 1 of Directive 2001/83/EC says: "In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications." The GL says that when comparability has been demonstrated in one therapeutic indication, extrapolation is the expectation. The exceptions are mentioned in the GL and should be considered in the justification by the Applicant.

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		the overall evidence provided from the comparability exercise and with adequate justification'.	
373-377	8	Comment: Please provide more detail regarding the acceptable means of justification for extrapolation. Proposed change: Consider amending the text as follows: 'Justification will depend on ……mechanisms of action of the active substance of the reference product in each indication (including its degree of certainty), and on receptors involved and on the reliability, sensitivity and validation of biological tests used to evaluate impact on it."	No. These issues are part of the routine assessment of comparability data.
373-377	14	Proposed change: "Justification will depend on ……mechanism of action of the active substance in each indication, receptors involved and on the reliability, sensitivity and validation of biological tests used to evaluate impact on target."	No. These issues are part of the routine assessment of the comparability data.
373-377	20	Comment: ("In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. Justification will depend on, e.g., clinical experience, available literature data, mechanisms of	No. All differences between the therapeutic indications are not relevant for the extrapolation. As pointed out, the concept of "most sensitive" is problematic because one therapeutic indication may not be most sensitive in all aspects safety, efficacy and immunogenicity. However, it makes no sense to test them in different populations. Thus, it is sufficient that the chosen population/model is sensitive to demonstrate differences in the various aspects. The situations where

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		action of the active substance of the reference product in each indication (including its degree of certainty), and on receptors involved.") : We agree that an applicant must provide separate justification or demonstration of a biosimilar's safety and efficacy "for each of the claimed indications" for which that applicant seeks marketing authorisation. To justify extrapolation, an applicant should also address potential differences in mechanism(s) of action and other factors that may differ between indications (such as pharmacokinetics, bio-distribution, and expected toxicities). The final guideline should also indicate that the applicant should consider whether the indication tested clinically is the most sensitive. We believe that extrapolation should be permitted only when the setting that has been studied clinically is as sensitive to any potential clinically meaningful differences between the products as the target indication for which licensure is sought on the basis of extrapolation. When the proposed new use may be more sensitive to clinically significant differences that cannot be excluded through analytic testing, additional clinical testing should generally be conducted. As noted above, identifying a single "most sensitive" indication may not always be possible, so applicants should consider whether testing in more than indication is warranted.	extrapolation may need additional data are mentioned in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
373-388	8	Comment: Please provide additional detail on the acceptable means of justifying extrapolation. Proposed change: Consider adding the following sentence at the end of this section: 'When applicant seeks indication extrapolation, the principle related to the conduct of efficacy and safety trials in the most sensitive population is of prominent importance and should be carefully justified for each indication."	No, the current text is sufficient to cover the need for justifications. The concept of a "most sensitive" indication or population is theoretical and usually not feasible when applied for all relevant features; pharmacokinetics, efficacy, safety and immunogenicity.
373-388	14	Comment: What seems to be missing from this section is whether there is a distinction between extrapolation between indications versus extrapolation within an indication to a new patient population e.g. paediatric studies. Proposed change: Consider whether adding this distinction would provide value and, if so, is the hurdle "lower" in some sense for the latter scenario i.e. extrapolation within an indication to a new patient population?	The Chapter 6 has been revised. The issue of different patient populations is primarily dealing with safety. Different patient populations are covered by the revised text. Specific safety issues may also be studied as part of the risk management plan.
373-388	14	Proposed change: We suggest inclusion of the following sentence, "When the applicant seeks indication extrapolation, the general	No, the current text is sufficient to cover the need for justifications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		principle related to the conduct of efficacy trials (5.3) in a sensitive population is of prominent importance and should be carefully justified."	
375-376	14	Comment: "In case the …..or, if necessary, demonstrated separately for each of the claimed indications" It is proposed to make the wording identical to the wording used in the mAb guideline. Proposed change: ~~In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications"~~ Extrapolation of clinical efficacy and safety data to other indications of the reference product, not specifically studied during the clinical development of the biosimilar, is possible based on the results of the overall evidence provided from the comparability exercise and with adequate justification.	No, the current modified text is sufficient to cover the topic. There is no discrepancy between this GL and the GL for biosimilar monoclonals.
377	15	Comment: We suggest the following revision Proposed change: … receptors involved and on the reliability, sensitivity	No. Reliability, sensitivity and validation are part of the routine assessment process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and validation of biological tests used to evaluate impact on target."	
377-380	16	Totally incomprehensible Proposed change: delete	The Chapter 6 has been revised.
379-380	8	Comment: Please provide additional detail on the acceptable means of justifying extrapolation. Proposed change: Consider amending the text as follows: 'This situation is not an argument for additional studies if the mechanism of action (MOA) in every indication as well as communalities of MOA across indications are well understood.'	No. The text refers to the response of different cells to the same signal provided via the same receptors. The purpose of the comparability studies should be to investigate the receptor binding using different methods..
379-380	14	Proposed change: "This situation is not an argument for additional studies if the MOA in every indication as well as communalities of MOA across indications are well understood."	The Chapter 6 has been revised. The text refers to the response of different cells to the same signal provided by the same receptors.
380-386	20	Comment: ("However, if there is evidence that different active sites of the reference product or different receptors of the target cells are involved in different therapeutic indications or that the safety profile of the product differs between the therapeutic indications, additional data may be needed to justify the extrapolation of	The Chapter 6 has been revised. The draft text gives the generalfactors that need to be considered when justifying the extrapolation. Basically, the knowledge of the reference product and its therapeutic indications, together with the results of the comparability exercise will guide the considerations related to extrapolation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		safety and efficacy from the indication studied in the pivotal clinical trial. For the extrapolation of safety, the Applicant should consider patient-related factors, such as different co-medication, co-morbidities, and immunological status, and disease-related factors, such as reactions related to the target cells, e.g. lysis of tumour cells.")**:** We agree that applicants should consider the patient-related factors set out in these lines. We encourage the CHMP to include in the final guideline a more detailed discussion of factors, some of which were mentioned in the Draft Guideline, that may influence the threshold question whether extrapolation is appropriate. The final guideline should also note that applicants will be expected to address all of these factors, which may make the setting of the new indication more sensitive to clinically meaningful differences: • *Immunocompetence*: Reduced immunocompetence in the studied population as compared to the target population (e.g., due to the disease state, such as cancer, or absence of use of concomitant medications, such as methotrexate, in the target population) may preclude detection of immunogenicity differences between the products in the target population. For example, pure red cell aplasia is a risk of erythropoietin use in renal failure patients that	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is rarely, if ever, observed in cancer patients. • *Susceptibility to toxicity*: Differences in underlying disease or other patient factors such as age may make the target population more sensitive to differences between the products with regard to toxicities. For example, patients with a predisposition to thrombosis due to their cancer may be more sensitive to increased thrombotic potential of a proposed biosimilar erythropoietin. • *Dosing*: Differences may manifest only at higher or lower doses, or differences may be more likely to emerge when dosing is intermittent rather than continuous or prolonged rather than short-term. For example, a higher dose and shorter dosing interval may inhibit immunogenicity, as has been observed with Remicade® (infliximab). • *Route of administration*: Differences between two products' bioavailability or immunogenicity profiles may emerge in one route of administration but not another. For example, differences between the immunogenicity profiles of a biosimilar erythropoietin product (sold under the names Binocrit, epoetin alfa Hexal, and Abseamed) authorized in Europe and its reference product (Eprex®) were not	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		observed with intravenous use but were observed with subcutaneous use. • *Concomitant medications*: Concomitant medications, which may vary by indication, may mask differences between the immunogenicity profiles or pharmacokinetics of the two products. The concomitant use of methotrexate, for example, affects infliximab's immunogenicity and pharmacokinetics. Concomitant medications also may increase sensitivity to toxicity differences. For example, the use of aspirin and heparin along with thrombolytic or anti-platelet biologics increases bleeding risk. The use of anti-tumor necrosis factor biologics with azathioprine or 6-mercaptopurinol in Crohn's Disease is associated with hepatospenic T-cell lymphoma, a condition rarely (if ever) seen in rheumatoid arthritis. • *Mechanism of action*: Where the mechanisms of action of a drug are not well understood or vary between two indications, extrapolation would be risky. For example, if a monoclonal antibody product's efficacy in the studied indication requires antigen binding but the target indication also requires Fc receptor activation, the study would not be sensitive to detect differences in Fc receptor activation.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Efficacy differences in the target indication might thus become apparent only after authorisation and clinical use. We recommend that the final guideline state that, in general, extrapolation should be considered only between indications in which the mechanisms of action can be characterized and are the same. Uncertainty about the mechanism of action or known differences in mechanism of action should preclude extrapolation. • *Pharmacokinetics and bio-distribution*: An applicant should in general demonstrate that there are no significant differences between the pharmacokinetics and bio-distribution of the product in the indication and population studied clinically and the indication(s) and population(s) for which licensure is sought on the basis of extrapolation. If the new patient population differs with regard to factors that may influence pharmacokinetics or increase sensitivity to differences between the products, the applicant should study its product in this population. Further, if the diseases require drug effect in different tissues (e.g., skin, joint, or gastrointestinal tract), it will be critical to ensure that the product is distributed similarly into the relevant tissues.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
384	15	Comment: We suggest to add the sentences in red as follows Proposed change: It might be necessary to carry out immunogenicity studies in each clinical indication because immune responses can be generated differently depending on the disease and the seriousness of the clinical consequences of any response. For the extrapolation of safety, the Applicant should consider patient-related factors, such as different co-medication, co-morbidities, and immunological status, and disease-related factors, such as reactions related to the target cells, e.g. lysis of tumour cells.	No. Immunogenicity has been thoroughly tested in one therapeutic indication. There is no need to test other indications unless the knowledge of the reference product suggests potential unique problems with immunogenicity. Testing immunogenicity outside a full-blown efficacy and safety study will usually not generate useful data for extrapolation.
386	9	Comment: Indications not studied, special patient groups (eg. young, old), particular patients with morbidities at greater risk, etc may be subject to PAE, PASS studies or patient registries. Proposed change: Post approval requirements can be PAE, PASS studies or patient registries agreed with the CHMP and include consultation of PRAC.	The proposed factors are already described in the guideline.
395-396	8	Comment: Please provide additional detail on the contents of the	Not accepted. For further guidance on the contents of the RMP please refer to the specific guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		risk management plan. Proposed change: Consider amending the text as follows: 'The risk management plan should take into account identified and potential risks associated with the use of the reference product, particularly those related to rare but serious adverse reactions, and, if applicable, additional potential risks identified during the development programme of the biosimilar and should detail how these issues will be addressed in post-marketing follow-up.'	
396-397	17	Comment: Would the identification of additional potential risks be compatible with biosimilarity? Proposed change: delete '~~*and, if applicable, additional potential risks identified during the development programme of the biosimilar*~~'	Accepted. This sentence has been deleted.
398	15	Comment: We suggest to add the sentences in red as follows Proposed change: Immunogenicity should specifically be addressed in this context, to assess the rate and consequences of immune responses, such as rare adverse events. Post-	Not accepted. This should be assessed on a case-by-case basis during the assessment of the RMP and the study protocol. In addition, the number of patients to be included in a post-marketing study is not specific for biosimilars but for all drugs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		marketing studies can require considerable numbers of patients if the occurrence of an adverse event is rare.	
398-400	1	Comment: BIO believes that any specific monitoring imposed on the reference product or product class should be included in the pharmacovigilance plan for the biosimilar product. Proposed change: "Within the pharmacovigilance plan, any specific safety monitoring imposed on the reference medicinal product or product class should be ~~taken into consideration~~ adequately addressed in the pharmacovigilance plan for the biosimilar product."	Accepted
398-400	8	Comment: Please provide additional detail on the contents of the risk management plan. Proposed change: Consider amending the text as follows: 'Within the pharmacovigilance plan, any specific safety monitoring imposed on the reference medicinal product or product class should be ~~taken into consideration~~ included in the pharmacovigilance plan for the biosimilar product.'	Accepted
398-400	14	Proposed change:	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"~~Within the pharmacovigilance plan, a~~Any specific safety monitoring imposed on the reference medicinal product or product class should be ~~taken into consideration~~ included in the pharmacovigilance plan for the biosimilar product."	
400	8	Comment: We suggest the following revision Proposed change ... product class should be included in the pharmacovigilance plan for the biosimilar product."	Accepted
400-403	8	Comment: The draft version of the guideline states that applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. We would like to draw EMA's attention to that there might be confidentiality reasons which might prevent the participation in already existing studies. It might well be that various applicants for a biosimilar products have different obligations in their RMP – due to the different data and studies contained in their applications. We have experienced difficulties if the details of the RMPs have to be shared across companies in order to come to a common protocol for these studies. Therefore, this encouragement should be treated with	Partly accepted. BMWP is aware of potential difficulties with the participation of biosimilar companies in already existing studies. Therefore, it is encouraged to participate. The sentence has been amended as follows: "Applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. However, new studies might have to be initiated."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		caution. Proposed change: Consider amending the text as follows: 'Applicants are encouraged, if confidentiality reasons allow it, to participate in already existing pharmacoepidemiological studies in place for the reference product or to apply similar epidemiological standards as are applied to the originator, if appropriate.'	
400-403	10	Comment: The draft version of the guideline states that applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. We would like to draw EMA to the attention that there might be confidentiality reasons which might prevent the participation in already existing studies. It might well be that various applicants for a biosimilar products have different obligations in their RMP – due to the different data and studies contained in their applications. We experienced difficulties if the details of the RMPs have to be shared across companies in order to come to a common protocol for these studies. Therefore, this encouragement should be treated with caution.	Please refer to the previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "Applicants are encouraged, if confidentiality reasons allow it, to participate in already existing pharmacoepidemiological studies in place for the reference product or to apply similar epidemiological standards as are applied to the originator, if appropriate."	
400-403	14	Comment: The draft version of the guideline states that applicants are encouraged to participate in already existing pharmacoepidemiological studies in place for the reference product. We would like to draw to the attention of EMA that there might be confidentiality reasons which might prevent the participation in already existing studies. It might well be that various applicants for a biosimilar products have different obligations in their RMP – due to the different data and studies contained in their applications. We experienced difficulties if the details of the RMPs have to be shared across companies in order to come to a common protocol for these studies. Therefore, this encouragement should be treated with caution. Proposed change: "Applicants are encouraged, if confidentiality reasons	Please refer to the previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allow it, to participate in already existing pharmacoepidemiological studies in place for the reference product or to apply similar epidemiological standards as are applied to the originator, if appropriate."	
401-403	8	Comment: "Risk minimisation activities in place for the reference medicinal product ……should also be included into the risk management programme of the biosimilar" There are situations (e.g. when the risk minimisation would be linked to the device used with the reference medicinal product) where this would not apply. The sentence should allow for that. Proposed change: Consider amending the text as follows: "Risk minimisation activities in place for the reference medicinal product should ***in principle*** also be included into the risk management programme of the biosimilar. Any deviation from this (e.g. when the risk minimisation would be linked to the device used with the reference medicinal product) should be justified."	Accepted.
401-403	14	Comment: "Risk minimisation activities in place for the reference medicinal product ……should also be included into the risk management programme of the biosimilar" There are situations (e.g. when the risk minimisation would	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be linked to the device used with the biosimilar) where this would not apply. The sentence should allow for that. Proposed change: "Risk minimisation activities in place for the reference medicinal product ……should in principle also be included into the risk management programme of the biosimilar. Any deviation from this should be justified."	
401-403	18	Comment: "Risk minimisation activities in place for the reference medicinal product ……should also be included into the risk management programme of the biosimilar" There are situations (e.g. when the risk minimisation would be linked to the device used with the biosimilar) where this would not apply. The sentence should allow for that. Proposed change: "Risk minimisation activities in place for the reference medicinal product ……should in principle also be included into the risk management programme of the biosimilar. Any deviation from this should be justified."	Accepted.
403	1	Comment: BIO recommends that the risk management plan include generation of sufficient safety data for any extrapolated indications.	Not accepted. This is beyond the scope of the biosimilarity exercise and is contradictive to the section on extrapolation of indications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "...programme of the biosimilar. If marketing authorization is granted on the basis of indication extrapolation, the risk management plan should include generation of sufficient safety data in the extrapolated populations."	
403	8	Comment: Please provide additional detail of the data to be generated in extrapolated populations Proposed change: Consider adding the following sentence: "If marketing authorization is granted on the basis of indication extrapolation, the risk management plan should include generation of sufficient safety data in the extrapolated populations."	Please refer to the previous comment.
403	15	Comment: We suggest inclusion of the following sentence Proposed change: "If marketing authorization is granted on the basis of indication extrapolation, the risk management plan should include generation of sufficient safety data in the extrapolated populations."	Please refer to the previous comment.
404-408	1	Comment:	Proper identification of the product administered to the patient is important as stated in the draft guideline. We also

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		BIO welcomes the Agency's reference to the need for clear product identification to facilitate pharmacovigilance monitoring. However, BIO recognizes that in practice batch numbers of medicinal products are often not recorded, and the recorded name is often the international non-proprietary name (INN), particularly in those countries that are required by law to prescribe by INN or in situations where the name consists of INN plus company name. BIO shares the Agency's concern for proper pharmacovigilance monitoring and believes that assigning unique INNs to all biologics should be a component of any strategy to facilitate robust, reliable pharmacovigilance monitoring.	acknowledge the concerns raised. In future, barcode controlled administration of drugs to patients will help the identification of the product administered. The discussion on INN's is beyond the remits of EMA and without the scope of this guideline.
404-408	2	Comment: It is appropriate and necessary that a clear identification of the concerned product is requested to support pharmacovigilance monitoring, namely the name of the specific medicinal product given to the patient and the batch number. These two elements provide the most sensitive/important information allowing the unambiguous identification of the finished medicinal product which is on the market in an EU member state and is in line with the newly adopted pharmacovigilance legislation (article 102 (e) of Directive 2001/83/EC as amended. It is welcomed that the brandname is not replaced by the INN because identifying the product by INN only	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would indeed not provide sufficient information in case of adverse event reporting, whereas the product/brand name as approved by the regulatory authorities and the batch number provide much more detail of the concerned product. The wording in the revised version of the guideline supports that the name of the active substance (the INN) can never fulfil the role of a unique product name which has been approved by regulators on the basis that it is not confused with other medicines. The INN is only used to identify the active substance of the medicinal product and has indeed no role in finished product traceability. Therefore, we strongly recommend that this language, in line with the newly adopted EU Pharmacovigilance legislation, remains unchanged in the final guideline.	
404-408	2	Comment: It is appropriate and necessary that a clear identification of the concerned product is requested to support pharmacovigilance monitoring, namely the name of the specific medicinal product given to the patient and the batch number. These two elements provide the most sensitive/important information allowing the unambiguous identification of the finished medicinal product which is on the market in an EU member state and is in line with the newly adopted pharmacovigilance legislation (article 102 (e) of Directive 2001/83/EC as amended.	Not accepted. The naming of biological products is outside the scope of this guideline.

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		We also suggest adding an additional final bullet point referring to the very recent COMMISSION IMPLEMENTING DIRECTIVE 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State. This directive stipulates that the brand name of a medicinal product should be used to ensure clear identification of biological medicinal products as defined in point 3.2.1.1.(b) of Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, because of the special characteristics of those products. Proposed change: Add an additional sentence after line 408: In order to support clear identification of prescribed and dispensed biological medicinal products, only brand names should be used for biological medicines in accordance with Commission Implementing Directive 2012/50/EU.	
404-408	10	Comment: It is very much welcomed that a clear identification of the concerned product is requested for suspected adverse reactions, namely the brand name of the medicinal product and the batch number. These two	General remark. No response required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		elements are indeed the most sensitive/important information playing the key role in the identification of the finished drug product which is on the market in an EU member state. Identifying the product by INN only would not provide sufficient information in case of adverse event reporting, since the product/brand name and the batch number provide much more detail of the concerned product.	
404-408	14	Comment: It is very much welcomed that a clear identification of the concerned product is requested for suspected adverse reactions, namely the brand name of the medicinal product and the batch number. It is recommended to add a reference to the EU legislation requirements. With the current naming conventions, identifying the product by INN only would not provide sufficient information. Nevertheless, we feel that an INN with a unique identifier (as currently under consideration by WHO) could play a role in providing additional global safeguard in case of adverse event reporting, on top of the product/brand name and the batch number. Proposed change: “Therefore, all appropriate measures should be taken to identify clearly any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal	Not accepted. Including a reference to the directive will not add to the scientific principles laid down in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product and the batch number as stipulated in Directive 2001/83/EC, article 102e.	
404-408	16	This is not a biosimilar specific issue but is true for all drugs **Proposed change:** delete	Accepted. This is, indeed not specific for biosimilars but for all drugs. However, this general topic is of specific importance to biological medicinal products, including biosimilars, and is therefore included in this guideline.
404-408	20	Comment: Postmarketing safety surveillance will be always necessary and will play a critical role in ensuring the safety of biosimilars after they have been approved. A biosimilar applicant's pharmacovigilance program should therefore continuously (1) monitor for safety signals (in larger and more diverse patient populations) that could not be detected through the premarket development program; and (2) monitor for signals that might arise from clinically significant changes in the product over time that may not be detected prior to batch release, including those caused by manufacturing changes or breakdowns in process. The final guideline should state that the CHMP may require a biosimilar applicant to conduct postmarketing studies (including, e.g., a long-term immunogenicity study), develop and maintain patient registries, engage in certain communications with healthcare professionals and patients, or take other postmarketing actions, depending on the safety questions concerning the biosimilar that remain when	The need for continuous monitoring of the safety profile of all drugs in general is acknowledged and is described in the relevant pharmacovigilance guidelines. Post-marketing changes to the production process should be handled for biosimilars in the same way as for all biologicals and will therefore not be specifically mentioned in this guideline. Naming and switching is outside the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the product is licensed (and regardless of the postmarketing commitments of the reference product sponsor). ("For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to identify clearly any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product and the batch number."): We agree that mechanisms should be in place to differentiate between adverse events associated with the biosimilar and adverse events associated with the reference product. We believe distinct (similar, but not the same) nonproprietary names for biosimilars are necessary to accomplish this objective. Also, where the products give rise to antibodies that react with different epitopes, the labeling should expressly warn against switching.	
408	8	Comment: We consider that changes in medication from an originator to a biosimilar or vice-versa or from biosimilar to an alternative biosimilar should be monitored as part of the risk management plan if possible.	Not accepted. The issue of switching is outside the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider adding the following text after the section. 'Changes in medication (originator to biosimilar etc) should be recorded in patient medical records.'	
408	14	Comment: To reflect the practical situation, please add as indicated Proposed change: "Any safety signals suggesting a deviation of the biosimilar product safety profile from the reference product will be subject to PRAC evaluation and recommendation."	Not accepted. This is current regulatory practice and does not add important information to this guideline.
409-411	8	Comment: While we do not consider that the principles of 'Switching' and 'interchange/interchanging' fall within the scope of this guidance and as such that there should not be discussion around the practices at a national level, we agree that it would be prudent to recommend that any data from switching and/or interchange is assessed during the review of adverse events and that the potential for switching should be mentioned in the risk management plan. Proposed change: Consider amending the text as follows:	The paragraph dealing with switching and interchangeability is outside the scope of this guideline and has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines that contain a given biological might occur. Thus,~~ Applicants ~~applicants~~ are recommended ~~to follow further development in the field and consider~~ to include the potential for switching ~~these aspects as~~ part of the risk management plan. ~~In addition, available.~~ Available data on switching should be carefully assessed during the review of adverse reaction reports.	
409-411	14	Comment: As indicated under general comments, we do not consider that the principles of 'switching' and 'interchange/interchanging' fall within the scope of this guidance. Proposed change: Consider amending the text as follows: ~~Depending on the handling of biosimilars and reference medicinal products 'switching' and 'interchanging' of medicines may or may not occur.~~ Applicants should consider the risk of switching medicines and carefully assess available data during the review of adverse reaction reports.	The paragraph dealing with switching and interchangeability has been deleted.
409-410	18	Reference to the EU legislation requirements might be helpful here.	The paragraph has been deleted.
409-411	1	Comment:	The paragraph dealing with switching and interchangeability

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		BIO does not consider that the principles of 'switching' and 'interchange/interchanging' fall within the scope of this guidance. Proposed change: "~~Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines that contain a given biological might occur. Thus, applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan. In addition, a~~ Available data on switching should be carefully assessed during the review of adverse reaction reports."	has been deleted.
409-412	10	Comment: Referring to "Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines that contain a given biological might occur. Thus, applicants are recommended to follow further development…", we agree that changes in medication should be monitored as part of the Risk Management Plan if possible. Proposed change: none	The paragraph dealing with switching and interchangeability has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
409-413	16	Unclear paragraph. Either clarify also by including precise definitions of interchange, substitution and switching or delete these statements.	The paragraph dealing with switching and interchangeability has been deleted.
411-413	18	This should be deleted – the recommendation given here is unclear and recommendations of switching or interchangeability are national matters which are out of scope of the EU Marketing Authorisation	The paragraph dealing with switching and interchangeability has been deleted.
412-413	2	Comment: We welcome that the EMA is interested in any available switching data of the biosimilar product. Gathering scientific information and practical experience on interchangeability is useful to generate a broader database to demonstrate that switches do not lead to increased risk. All available information thus far shows that no safety issues result from such product switches, which have been occuring frequently and broadly between epoetins, growth hormones, G-CSFs, insulins, interferons, and TNF alfa antagonists for many years(see publications on switching : Ebbers et al.: The safety of switching between therapeutic proteins Expert Opin. Biol. Ther., 2012; Gouw et al., N Engl J Med 2013; 368:231-239). Consequently, supported by all available information so far, biosimilars and their reference products can be considered interchangeable at the population level and an approved EU biosimilar product can be interchangeable in all approved therapeutic indications	The paragraph dealing with switching and interchangeability has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		under supervision of a health care professional.	
412-413	9	Comment: Normally it is the practice of many sponsors to generate some data switching all patients on originator to biosimilar during the open label extension phase of the study. A few sponsors are pursuing multiple switches back and forth originator/biosimilar with a view to claiming exclusitivity from the FDA for a 'second tier' biosimilar, that is what Congress forsees as the basis for US definition of interchangeability which would be pharmacy level substitution. But first a biosimilar approval along EU lines would be a prerequisite.	The paragraph dealing with switching and interchangeability has been deleted.
412-413	10	Comment: We welcome that EMA is interested in any available switching data of the biosimilar product. Gathering scientific information and practical experience on interchangeability is useful to generate a broader database to demonstrate that switches create no safety issues. All available information thus far shows that no safety issues result from such product switches, which have been occuring frequently and broadly between epoetins, growth hormones, G-CSFs, insulins, interferons, and TNF alfa antagonists for many years.	The paragraph dealing with switching and interchangeability has been deleted.
N/A	11	REFERENCES:	The guideline does not normally include references.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Berkowitz et al. (2012). Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nature Reviews Drug Discovery, 11(7): 527-540. Gascon et al. (2013). Clinical experience with Zarzio in Europe: what have we learned? Support Care Cancer, 21: 2925-2932. McCamish and Woollett. (2011). The state of the art in the development of biosimilars. Clinical Pharmacology and Therapeutics, 91(3): 405-417. Reinke. (2012). Biosimilars might not measure up to health plan expectations. http://managedcaremag.com/linkout/2012/10/12 Xu and Vugmeyster. (2012). Challenges and opportunities in absorption, distribution, metabolism and excretion studies of therapeutic biologics. The AAPS Journal, 14(4): 781-791	